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1937

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Extract from a letter in the BRITISH MEDICAL JOURNAL, August 11th, 1956. p. 374

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SIR HENEAGE OGILVIE, K.B.E., D.M., M.CH., F.R.C.S.

WILLIAM A. R. THOMSON, M.D.

JOSEPH GARLAND, M.D. (*Consultant Editor in U.S.A.*)

5 BENTINCK STREET, LONDON, W.1. WELBECK CI21

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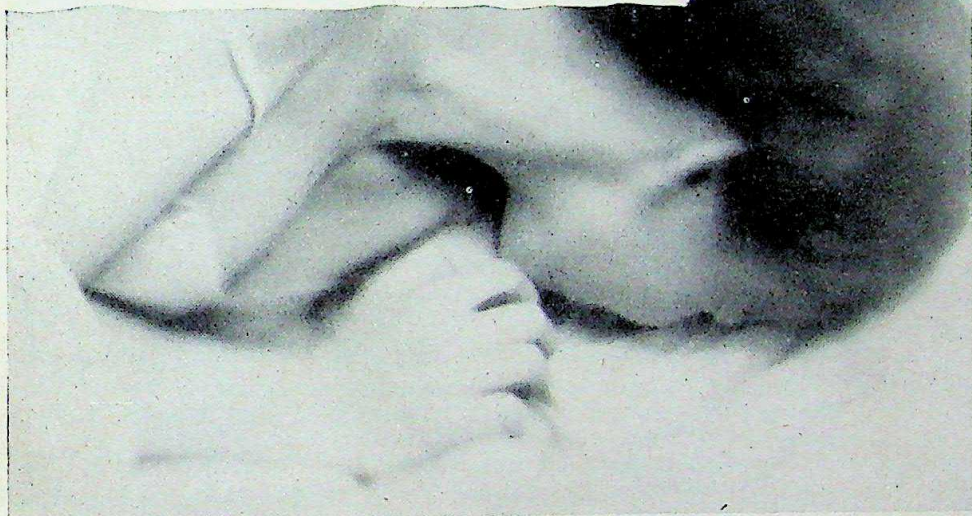
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GENETIC ASPECTS

Of the 69 families with classic hæmophilia, a sex-linked recessive pattern of transmission was present in 65 per cent., and among the 12 families

Screening test	If abnormal, proceed in sequence to
1. Clotting time and visual gross clot retraction.	Cross-protection test by prothrombin consumption or recalcification times and thromboplastin generation test.
2. Bleeding time.	Microscopic examination of capillaries, quantitative clot retraction and thromboplastin generation test.
3. Platelet count and examination of blood smear.	
4. Quick 'prothrombin' time.	Quantitative prothrombin, proconvertin, pro-accelerin and fibrinogen.
5. Prothrombin consumption.	Cross-protection test by prothrombin consumption or recalcification times, quantitative clot retraction and thromboplastin generation test.

TABLE II.—Screening tests performed on a patient suspected of having classic hæmophilia or related disorders.

All the tests in the *left column* are performed on a suspected 'bleeder' as screening procedures. If all are normal, the patient is considered normal provided that *his history is not strongly suggestive of a hæmorrhagic tendency*. 1 and 5 are abnormal in classic hæmophilia and Christmas disease, 2 in von Willebrand's disease. All may be normal in PTA. In either case, the procedures in the *right column* are performed as more refined tests to rule out minor abnormalities. (See text for interpretation).

with Christmas disease, in 60 per cent. The abnormality in each is transmitted through female 'carriers' and is manifested in affected males.

These figures are in agreement with other published series (Biggs and MacFarlane, 1953) and indicate that in over a third of all such children, the defect has occurred in the presently studied generation without a positive family history. Some investigators, e.g. Andreassen, 1943, have suggested, but others have refuted (Mersky and Macfarlane, 1951), that mild degrees of AHF deficiency may occur in female siblings and that by proper techniques those females who are 'carriers' may be identified. Although several of our patients' mothers have suggestive histories of abnormal bleeding and have shown slight but reproducible defects in the generation of thromboplastin, we do not feel that our evidence is statistically valid to predict this defect in female carriers. Severe classic hæmophilia has been reported in females in whose families both parents apparently possess the defective gene (Israëls *et al.*, 1951). We have not encountered such a case. The severity of the coagulation defect remains the same throughout the patient's life and usually is manifested to similar degree in affected siblings. Mild forms of AHF and PTC deficiency have been studied in which an allelic form of the defective gene is postulated (Brinkhous *et al.*, 1954). These patients usually do not manifest serious bleeding tendencies except under stress and may have an almost normal clotting time. Eleven of our children with classic hæmophilia and six with Christmas disease fall within these groups. The amount of AHF may vary between 3 to 10 per cent. of normal adult levels. We have not measured the degree of Christmas factor deficiency.

PTA deficiency, on the other hand, appears to be transmitted by a Mendelian dominant gene with incomplete penetrance (Rosenthal *et al.*, 1953). In one of our two families with this disease, the mother and one of three children have histories of abnormal bleeding and characteristic thromboplastin generation tests. We have little evidence for the genetic

transmission of von Willebrand's disease ('pseudohæmophilia'), although in one family the father and the only son are affected. A Mendelian dominant type of inheritance has been postulated (MacFarlane, 1941).

CLASSIC HÆMOPHILIA AND CHRISTMAS DISEASE

The clinical manifestations of classic hæmophilia and Christmas disease are almost identical. It was only upon administering blood from one patient to

Type of abnormal bleeding	Incidence in 94 patients (per cent.)	Type of abnormal bleeding	Incidence in 94 patients (per cent.)
Dental extractions (27 patients)	100	With development or loss or primary dentition	21
Appendicectomy, tracheotomy and other operative procedures	100	Severe hæmorrhage into tissues of neck	18
'Easy bruising'	90	Following infection	15
Hæmarthroses	90	Following dental extraction	3
Intramuscular	82	Nervous system	16
Epistaxes—repeated	67	Peripheral nerve palsy	9
Mucous membranes of mouth, tongue, and frenulum	60	arm:ulnar nerve	3
Neonatal period (29 patients)	35	leg:femoral, lateral femoral cutaneous nerves	6
Following circumcision	32	Central nervous system	7
Intracranial	2	Gastro-intestinal	10
Umbilical	1	Mortality	
Genito-urinary	26	Severe intracranial hæmorrhage—2 patients	
Intra-abdominal and retro-peritoneal	24	During tracheotomy for severe hæmorrhage into neck—1 patient	
With development or loss of permanent dentition	24		

TABLE III.—Incidence of clinical manifestations in 94 patients with classic hæmophilia and Christmas disease.

another (both of whom were considered to have classic hæmophilia) and finding mutual correction of their defects, that the difference between these two diseases was first recognized (Pavlovsky, 1947; Schulman and Smith, 1952). The following findings (table III) include the clinical manifestations of these conditions in 80 patients with classic hæmophilia (also termed hæmophilia A) and 14 with Christmas disease (also termed hæmophilia B).

BLEEDING IN INFANCY

Since these diseases are congenital, it is not unusual that 35 per cent. of the infants manifested abnormal bleeding tendencies within the first ten days of life. Antihæmophilic factor is absent from the cord blood of a child with this defect. One infant bled from the umbilicus, two had intracranial hæmorrhage and 26 bled following circumcision. The latter is often severe enough to require plasma or whole blood administration (four cases with mild classic hæmophilia and two with congenital PTC deficiency had no abnormal bleeding with, or following, circumcision). These infants also

have physiologically low Christmas factor, prothrombin and proconvertin levels and poor formation of thromboplastin. Their protected environment undoubtedly lessens the high risk of hæmorrhage.

During the first three years of life 60 per cent. of these patients have had prolonged bleeding from small lacerations of the lips or mucous membranes of the mouth. Such lesions are apt to bleed for several days. Constant washing with saliva prevents adequate hæmostasis and the clots are soft and fragile. We admit these infants to hospital, and administer sedatives and plasma infusions for three days or until adequate clot formation has occurred. An attempt is made to keep the bleeding area dry and free of saliva but in small children, local hæmostatic measures are often difficult to apply. Ice applied to a bleeding area in the mouth has often delayed adequate clot formation and prolonged the bleeding. Two children first developed subcutaneous hæmatomas following immunization injections. We recommend that each child receive routine immunizations but that these be given carefully; with local application of ice and pressure dressing no untoward reactions have occurred.

DENTAL CARE AND EXTRACTIONS

Appearance and loss of decidual teeth infrequently caused prolonged bleeding and could be handled by local application of hæmostatic agents. Early and adequate dental prophylaxis is important, for extraction of teeth with resultant tearing of tissue has caused severe and dangerous bleeding. We urge that all patients have regular dental examinations after their second year of life. Occasionally the gums bleed from vigorous brushing; this usually stops spontaneously.

Twenty-two children have had extraction of teeth for caries. Since the institution of planned therapy, complications from this procedure have been unusual. Should extraction be necessary, the patient is admitted to the hospital and given plasma infusions immediately before, during and for two to four days afterwards. Gentle surgical care is exercised and the tooth socket is packed with 'gelfoam' or 'oxycel' soaked in a concentrated solution of 'topical thrombin (bovine)'. At times gentle manual pressure must be maintained over the socket for several hours. Prostheses and other mechanical devices designed to maintain pressure over the area (Birch, 1937; Davidson *et al.*, 1949) have not been practical in small children. The patient is given nothing by mouth. Should bleeding occur, it usually happens during the second or third day after extraction. The inadequate soft clots are then completely removed, a new freshly prepared pack is introduced and plasma is administered for two more days. An attempt may be made to keep the area dry with cotton packs and suction. On the third day, a fluid diet is started. The potential danger from bleeding is not passed until after the 6th day.

Suturing of a bleeding area or the margins of the socket is distinctly *contraindicated*.

GASTRO-INTESTINAL AND GENITOURINARY BLEEDING

Gastro-intestinal hæmorrhage is unusual (10 per cent.) and mild, even when associated with diarrhoea, in infancy. Rarely it may be difficult to control. Bed rest, antispasmodics, and continuous whole blood and plasma infusions tided one child over a three-week period of massive melæna. A suspected peptic ulcer healed with medical treatment. Hæmaturia (26 per cent.) may follow trauma to the renal area and occurs mainly in those with severe clotting defects. Despite plasma infusions such hæmorrhage usually lasted ten days to two weeks. Recently, we have been able to reduce this period by combining oral cortisone with plasma infusions.

BLEEDING INTO CRANIUM OR NECK

Hæmorrhage into or around the brain following trauma (7 per cent.) and into the soft tissues of the neck (18 per cent.) secondary to croup, severe pharyngeal infections and massive bleeding into tissues following dental extraction (3 per cent.) are major complications. Absolute bed rest, constant plasma infusions and, at times, steroid therapy, combined with fine surgical judgment, must be used in every such situation. Even so serious a problem as that of a 4-month-old infant with a fracture of the skull and massive repeated subdural and epidural hæmatomas was recently treated successfully with plasma infusions and surgical intervention. Of the three deaths in this series, two followed intracortical brain hæmorrhage secondary to severe trauma (Chalgren, 1953) and one resulted from tracheal compression, the child having arrived at the hospital *in extremis*. In the case of bleeding into the neck, care must be taken that an adequate airway is always present. All except three cases with such complications were associated with inadequately treated pyogenic pharyngeal infections and occurred on the 2nd to 4th day of illness. Our patients are strongly urged to seek medical attention at the earliest sign of any infection, since their tendency to bleed is increased during this time.

SURGICAL PROCEDURES

Two children have survived tracheotomy, although we are reluctant to perform this procedure and have successfully used medical measures alone in the last eight instances of pharyngeal bleeding. Constant nursing care and close observation are necessary. We have not employed intubation (MacDonald *et al.*, 1953) for fear of increasing local hæmorrhage. Three others have undergone successful appendicectomies while receiving continuous fresh-frozen plasma infusions. Two of these developed minor post-operative bleeding into the wound.

In cases in which surgical treatment is necessary, we believe that these children should be treated as one would a patient without hæmophilia, provided the hæmophiliac is receiving adequate constant replacement therapy with plasma. No deaths have occurred as a result of surgery. Our experiences do not agree with the previously reported major surgical mor-

ality of 20 to 35 per cent. in hæmophiliacs (Davidson *et al.*, 1949; MacDonald *et al.*, 1953).

BLEEDING INTO JOINTS

The most common site of serious repeated hæmorrhage in these patients is into the large joint cavities of their extremities: 85 per cent. have experienced such episodes first occurring between 18 months and 3 years of age. Most often such bleeding follows a twisting injury which is often unnoticed by the patient. All our patients with classic hæmophilia, and 10 of the 14 with Christmas disease, have had hæmarthroses after 6 years of age. Of the group with classic hæmophilia, 15 per cent. are less than 3 years of age and of these, half have not had joint hæmorrhages.

At the first symptom of pain, we urge that the patient rest the extremity and curtail weight bearing. Should the signs of hæmorrhage continue, the child is seen together by the medical and orthopædic services in this hospital and his care remains their mutual responsibility. In all cases, initial coagulation studies are performed to substantiate the diagnosis of a hæmorrhagic disease and its response to plasma. With slight bleeding, the joint is placed at rest by immobilizing the extremity in a bivalved plaster case. If a large hæmorrhage is present, the child is admitted to the orthopædic ward where blood may be aspirated from the joint under local or general anaesthesia. Our experience with agents to increase the absorption of blood (hyaluronidase) has not been impressively different from that employing aspiration alone. Plasma infusions are begun at the time of aspiration and continued at six-hour intervals until signs of active bleeding have diminished. These signs are objective—from the size of the joint—and subjective—from the disappearance of pain without the joint cavity. A pressure dressing or a plaster cast, which is soon bivalved, is applied to provide an initial phase of complete immobilization and rest. Ice packs, sedation and, rarely, narcotics may be necessary to relieve pain. Cold packs may also diminish further local hæmorrhage through vasoconstriction.

Several days after bleeding has stopped, gentle passive physiotherapy is begun to prevent the development of joint contractures. If hæmorrhage into the joint cavity and surrounding tissues causes sufficient muscle spasm to produce flexion deformity, gentle traction (up to 4 to 6 lb. [1.8 to 2.7 kg.]) is applied to restore motion and alignment. Weight bearing should be avoided for several weeks or months through the use of orthopædic aids. It is felt that the first hæmorrhage causes structural damage which may heal completely with restoration of normal joint function. Repeated hæmarthroses into the same area (which occur before the previous one has had time to heal completely) lead to destruction of joint cartilage and serious ankylosis. Such periods of forced immobility are difficult for the young child to understand and create trying times for the parents. Unfortunately, despite these measures about 40 per cent. of our patients who have had repeated hæmarthroses have developed moderate to severe functional impairment.

BLEEDING INTO MUSCLES

Small hæmorrhages into muscles are usually not serious and are treated with plasma infusions and pressure dressings. Hæmorrhage into a deep fascial compartment containing blood vessels and nerves, on the other hand, causes intense pain and protective flexion may result in ischæmia of the distal parts and irreparable damage to the nerves. This is akin to Volkmann's ischæmic paralysis. The swelling is deep within the tissues and difficult to palpate. It should be recognized early.

With large hæmorrhages it is advisable to attempt to evacuate blood by aspiration if localized collections are present. Whether or not surgical incision and drainage should be employed depends upon the individual patient's condition. Early treatment, consisting of plasma infusions, bed rest, elevation and immobilization of the extremity in plaster casts, has prevented most such complications during recent years. Physiotherapy is started early and function may return gradually over a period of months. Two patients had developed ischæmic paralysis of the arms before being seen here. Two others have suffered femoral nerve palsies from hæmorrhage beneath the inguinal ligament.

NOSE BLEEDS

Nose bleeds, though frequent, have seldom been serious. The bleeding point is visualized and small 'gelfoam' packs soaked in 'topical thrombin' solutions are applied with gentle pressure. The cautery should not be used since destruction of tissue by this means usually leads to further bleeding.

LACERATIONS AND SUBCUTANEOUS HÆMATOMAS

Lacerations are not sutured unless the patient is receiving replacement therapy, because needle holes often present additional points from which bleeding develops later. A simple cut may be treated with pressure dressings left on for four to six days. Often the initial bleeding of such clean lacerations stops fairly soon, only to recur several times over the ensuing days unless pressure is applied constantly. On occasion powdered 'topical thrombin' may improve hæmostasis. An infected wound should be treated similarly and with intensive chemotherapy.

Bruises and *subcutaneous hæmatomas* require no treatment unless severe continued bleeding results. In the latter case, plasma infusions are given; on occasion once or twice daily for three days to tide the child over the acute episode.

Drugs are preferably given by mouth or vein, as hypodermic or intramuscular injections may lead to hæmatomas. Since the tissues of these patients contain a normal amount of thromboplastic substance ('tissue thromboplastin'), venepuncture sites seldom bleed provided adequate pressure is applied immediately and for at least five minutes after withdrawing the needle from the vein. Deep veins, particularly the femoral, should not be used for venepuncture lest the vein wall be lacerated and

massive hæmorrhage result. In one case of attempted femoral puncture in a suspected hæmophilic patient, obstruction to venous return persisted for several days and led to a Volkmann's type of contracture.

It has been stated both by other workers (Birch, 1937), and at times by the children's parents, that increased frequency of hæmorrhage occurs most often during the spring of the year. We have noted that many children pass through 'bleeding phases' when for months on end they appear to bruise more easily and to develop hæmarthroses more frequently. In 35 per cent. of cases such bleeding phases were associated with infections; usually mild upper respiratory ones. A review of 22 patients with repeated admissions to hospital indicated that 10 were admitted more often in the spring of the year, and 12 at other times. It is probable that the increased activity of a growing boy during the spring, and possible changes in the vascular structure of these patients (Pavlovsky, 1947), result in increased bleeding episodes. We have been unable to correlate the occurrence of such 'bleeding phases' with any other events.

REFRACTORY PATIENTS

Infrequently, patients with hæmophilia or with Christmas disease who have received infusions of plasma become refractory to the effect of this replacement therapy (Munro and Jones, 1943; Frommeyer *et al.*, 1950). Three children with classic hæmophilia and one with Christmas disease (4 per cent.) have been resistant for six, five, four and two years, respectively, and have remained so despite the discontinuance of plasma administration for the past eighteen months. All the children, at one time, responded normally to replacement therapy and the cause for their refractoriness is unknown. In one case of Christmas disease the resistance was lost temporarily.

It has been postulated that antibodies to AHF develop in these resistant patients. We have readily demonstrated a potent inhibitor to the action of AHF in their plasma. In contrast to the findings of others (Frommeyer *et al.*, 1950; Craddock and Lawrence, 1947), however, we have been unable to demonstrate a precipitin reaction by layering these plasmas with a solution of Fraction I. Although this anticoagulant activity may be in the gamma globulin fraction (Craddock and Lawrence, 1947), it is altered by clotting, for such activity is lessened in the patient's serum. It has been suggested that massive replacement therapy may overcome the action of this inhibitor (Frommeyer *et al.*, 1950). In one bleeding resistant patient we have been unsuccessful in lowering the clotting time by such treatment since, in such cases, AHF is probably utilized more rapidly than normally.

Twenty-three children have received Fraction I. Two patients with classic hæmophilia who subsequently became resistant are in this group. The resistant patient with Christmas disease received Fraction I which contains no Christmas factor. One child has become refractory who has never been given Fraction I. From this data it seems unlikely that Fraction I is instrumental in causing resistance as has been recently suggested (Alexander, 1955). Many children (62 per cent.) have received over 50 different plasma infusions, some up to 30 litres of plasma, without developing resistance. Why a few of the children of this group (4 per cent.) develop such an

inhibitor against AHF or PTC remains an enigma. We feel that plasma should be administered in limited but adequate amounts and only for severe bleeding episodes. The risk of development of resistance must be balanced by the risk of severe blood loss or development of orthopaedic deformity. Large doses of cortisone (300 mg. twice daily) or corticotrophin (75 mg. twice daily) lessen the severity of bleeding clinically, probably through a vasoconstrictor effect on small blood vessels. In our experience, these steroids have no effect upon the clotting mechanism in either the usual or resistant patient. No change in clotting time, prothrombin consumption or the thromboplastin generation test occurred in the four resistant patients who were given cortisone for five days and then a single infusion of fresh plasma (2 to 4 ml. per lb. [4.5 to 9 ml. per kg.]). The care and treatment of these patients is extremely difficult.

PLASMA THROMBOPLASTIN ANTECEDENT DEFICIENCY

The clinical features of patients with plasma thromboplastin antecedent (PTA) deficiency differ from those described, in that manifestations of abnormal bleeding are milder and occur primarily under surgical stress such as dental extraction, tonsillectomy, and abdominal operations and in minor episodes, such as slightly increased tendency to bruise and frequent nose bleeds. Clotting times were normal or slightly prolonged to 18 minutes, prothrombin consumption was normal and all other coagulation studies except the thromboplastin generation test fell within normal control values. In the latter, platelet function was likewise normal and the defect was partially corrected by the substitution of either normal barium sulphate-treated-plasma or normal serum. Characteristic findings such as these have been reported by Rosenthal *et al.* (1953).

VON WILLEBRAND'S DISEASE (PSEUDOHÆMOPHILIA)

The children within this group characteristically have prolonged bleeding-time determinations and prolonged bleeding following lacerations of the mouth in infancy, frequent nose bleeds and hæmorrhage following surgical operations. These abnormalities are due to a combined defect in capillary structure with poor retractability (MacFarlane, 1941) and in thromboplastin generation with varying degrees of AHF deficiency. This latter finding was first reported by Alexander and Goldstein (1953). In our three patients AHF levels range from 20 to 60 per cent. of normal. These levels are probably adequate for normal hæmostasis but, when combined with the vascular defect which appears to be the prime abnormality, may complement the bleeding tendency. In our experience, treatment with cortisone and plasma infusions has halted bleeding within twenty-four to forty-eight hours.

PLASMA THERAPY

It is possible to provide the missing blood component and lower the clotting time of blood in these patients by the intravenous administration of plasma from a normal person. We have used single donor's blood rather than

plasma because of the inherent danger of transmission of serum hepatitis virus. Even though moderate AHF potency may remain in carefully drawn blood for one week when stored at 4°C. (Brinkhous, 1954), it often begins to disappear within several hours. We have not relied on such bank plasma for the treatment of bleeding in patients with classic hæmophilia. AHF, however, remains active for several months in plasma which is freshly frozen at -20°C. or specially dried (dried antihæmophilic plasma, Hyland Laboratories, Pasadena, California). It is essential therefore to separate and freeze the plasma for storage within an hour after the blood has been drawn. As it is required, the material is thawed and administered to the bleeding patient. Plasma, in amounts of 1 to 2 ml. per lb. (2.2 to 4.5 ml. per kg.), is given by intravenous drip every six hours until the bleeding stops. Even this may not be adequate in one-dose amounts, but its effect becomes cumulative and from clinical and laboratory experience such treatment is satisfactory in the patient who is not actively losing blood. In the latter case and in conditions of critical nature, larger amounts have been used and administered continuously, and fresh whole blood may be needed to replace lost red cell mass.

The missing factor in Christmas disease and PTA deficiency remains active in conventionally stored or dried bank plasma for several months. Since this type of plasma is readily available, it is important to differentiate these diseases from classic hæmophilia. Some effect of these substances also remains in the blood of patients for up to ten days. In those with Christmas factor deficiency, we therefore administer bank plasma in doses of 2 ml. per lb. (2.2 to 4.5 ml. per kg.) at twelve to twenty-four hourly intervals.

Plasma should be obtained from a donor of the same ABO and Rh type if possible. After repeated administration, sensitization or plasma reaction may occur if the blood type of the donor is different from that of the recipient. Type O plasma from a 'universal donor' should be neutralized with Witebsky's substances to inactivate some of the saline-active naturally occurring antibodies (1 ml. per 50 ml. of plasma). Plasma is not drawn from persons with a previous history of jaundice, malaria or other diseases transmitted via blood.

In an attempt to prevent hæmorrhagic episodes, prophylactic therapy has been utilized by Alexander and Landweehr (1948) in severe cases (administration of plasma thrice weekly). We have used such a plan occasionally and feel that it is partially successful. The economic problems involved, however, and the possibility of the development of resistance have precluded its use on a large scale and our limited experience does not allow adequate evaluation of this plan.

In small children the amount of bleeding into tissues and joints is often sufficient to produce a rapidly developing anæmia and, at times, shock from blood loss. Fresh whole blood for the patient with classic hæmophilia or von Willebrand's disease, or bank blood for those with Christmas disease or PTA deficiency, must be given to supply red cells in addition to plasma.

We transfuse a child who is bleeding with whole blood when his hæmoglobin drops below 7 grammes.

LOCAL HÆMOSTATIC AGENTS

Oxidized cellulose ('oxycel'), gelatin by-products ('gelfoam') and other materials exert a local hæmostatic effect by hastening coagulation and apparently by-passing the abnormal physiological mechanisms in these children (Seegers and Sharp, 1948). These are clinically effective if placed directly on the bleeding vessel; they are of little use if packed above an already partially formed but poor clot. More potent and physiologically active is commercially prepared bovine thrombin ('topical thrombin') which may be applied locally as a powder or in solution. Our most useful combination of these agents is 'oxycel' soaked in thrombin solution. Fibrin foam and human thrombin are avoided because of the possible transmission of serum hepatitis virus (Porter *et al.*, 1953).

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PURPURA

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By purpura we mean non-traumatic subcutaneous hæmorrhages varying in size from pin-point petechiæ to large ecchymoses an inch or more across. There are two main groups of purpuric disease: (1) those in which abnormalities of the blood are present and abnormalities of the blood vessels are less important; (2) those in which abnormalities of the blood vessels occur, but the blood itself is normal. Humble (1949) has pointed out that the reason why these two groups both produce subcutaneous purpura is that the leak of blood into the tissues occurs at the same point: the junction between the smallest arteriole and the first capillary blood vessel. But otherwise the two groups, usually known as thrombocytopenic purpura and anaphylactoid purpura, present different clinical pictures, pursue a different clinical course, and require different management. The main differences are set out in table 1.

ETIOLOGY OF THROMBOCYTOPENIC PURPURA

Purpura is liable to occur when the blood platelets are depressed below about 40,000 per c.mm. (normal 250,000 per c.mm.). There are two main groups of thrombocytopenic purpura:—

(1) Primary thrombocytopenic purpura in which the cause is still not known.

(2) Secondary thrombocytopenic purpura. In this group the thrombocytopenia and the purpuric rash are caused by: (a) other blood diseases, such as acute leukæmia, aplastic anæmia or reticuloses; or (b) toxic substances, particularly drugs such as phenylbutazone ('butazolidin'), gold, chloramphenicol and sometimes barbiturates. The diuretic, acetazolamide ('diamox'), is the latest addition to the list. Benzol poisoning is given as a cause in all textbooks, but is now very unusual.

The most popular idea is that thrombocytopenic purpura is a form of hypersplenism in which the spleen collects and destroys the circulating platelets more rapidly than usual. The resultant call for more and more platelets is met by hyperplasia of the platelet-forming megakaryocytes in the bone marrow. The good results of removal of the spleen, even though it is rarely more than three times normal size (and therefore not palpably enlarged) confirms this hypothesis. But hypersplenism has never been accepted as a complete answer. Some patients fail to respond to splenectomy when no other primary disease can be found; some patients have thrombocytopenia without hæmorrhages or obvious ill-effect.

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Another possible cause was put forward by Ackroyd (1953) who showed that the thrombocytopenic purpura caused by the drug, 'sedormid', was due to the development in the blood of an antibody that destroyed platelets. Thrombocytopenia is often found in acquired hæmolytic anæmia—a disease due to antibody destruction of red blood cells. Techniques were devised

	Thrombocytopenic purpura	Anaphylactoid purpura
Type of rash	Small, reddish-purple spots or large purple areas	Fine, bright-red rash often preceded by swelling, large areas may start as urticaria
Pain in rash	Lesions painless	Lesions painful to pressure, often preceded by itching
Bleeding from mucous membranes	Common from mouth, nose, vagina	Unusual, sometimes in small intestine
Joints	Unaffected	Sometimes painful and swollen
C.N.S. hæmorrhage	Recognized complication	Very rare
Blood count	Platelets low (10,000 to 30,000 per c.mm.)	Platelets normal
Bleeding time	Always prolonged	Sometimes prolonged
Capillary fragility	Hess test positive	Hess test often negative, but Scarborough test positive
Course	Either remits in 3 to 4 weeks or becomes chronic	Recurrent crops of petechiæ for a few weeks, or very chronic course lasting for years
Treatment	Cortisone, prednisolone; or if these fail, splenectomy	Cortisone, prednisolone, or antihistamine drugs
Results of treatment	Very good	Poor, if no spontaneous remission
Occurrence secondary to other blood diseases	Yes	No

TABLE 1.—Differences between thrombocytopenic and anaphylactoid purpura.

for the detection of anti-platelet antibodies in the circulating blood of patients with thrombocytopenic purpura, and at first the results showed that there were such antibodies present in a fair proportion of cases. This suggested that, if antibodies were present, treatment with cortisone would be correct, whereas if they were not present, splenectomy would be indicated. Unfortunately more experience has denied us this attractively simple guide. Patients who have failed to respond to splenectomy may have no

anti-platelet antibodies, and patients who had responded were found to have these antibodies present, even postoperatively. The tests are awkward to carry out and difficult to interpret; antibodies have been detected, by these tests, in the blood of patients who had never had purpura. Consequently, although it is quite likely that platelet antibodies play some part in the etiology of thrombocytopenic purpura, their exact role is as yet uncertain.

DIAGNOSIS OF THROMBOCYTOPENIC PURPURA

The presence of so many potentially serious causes of thrombocytopenia means that before a case can be confidently labelled 'primary', other possible causes must be excluded. Some clues are available from the clinical examination. Severe and obvious anæmia is not often caused by primary purpura; a palpably enlarged spleen is suggestive of leukæmia or reticulosis and is hardly ever found in primary purpura.

The diagnosis, however, is nearly always settled by the laboratory studies of which two are essential: the blood count and examination, and a bone-marrow aspiration biopsy. The blood count will show low platelets and, in some patients with acute leukæmia, the presence of abnormal leucocytes in the peripheral blood will give the diagnosis at once. In other patients the next step is a bone-marrow biopsy; in adults and children over 15 years old, sternal marrow is best; in children under 15 years old I prefer an iliac crest biopsy. The procedure is quite safe and will not cause hæmorrhage provided that pressure is maintained on the puncture site till bleeding really stops, and this may take two minutes or so. Bone-marrow biopsy distinguishes at once the cases which are due to acute leukæmia and aplastic anæmia; in the leukæmias the marrow will contain many abnormal and primitive leucocytes; in aplastic anæmia the marrow will be much less cellular than usual, erythroblasts and granulocytes being relatively few and megakaryocytes absent. In primary thrombocytopenic purpura the bone marrow shows a normoblastic hyperplasia—a response to loss of blood—with often granulocyte activity as well. The megakaryocytes are often increased in number and forms without platelet formation and immature forms may be seen; but neither of these unusual forms needs to be seen to ensure a diagnosis of primary thrombocytopenic purpura. Some megakaryocytes should be found because if they are not, response to treatment is liable to be disappointing.

In every case it is most important to inquire about drugs, and here the general practitioner should always tell the consultant what drugs the patient has been having during the previous three months, not forgetting barbiturates as even phenobarbitone has been known to cause thrombocytopenia, and the new 'tranquillizers' must be regarded as potentially toxic too. No patient with a recent history of taking drugs that can cause thrombocytopenia is treated by splenectomy.

MANAGEMENT OF THROMBOCYTOPENIC PURPURA

The commonest clinical presentation is the appearance of purpura with perhaps a little bleeding from some mucous membranes; the general condition of the patient is good. If the history is short, at most a few weeks, a 'wait and see' policy is best, especially in children and young women up to the age of 25, because spontaneous remission, often permanent, occurs in a fair proportion of patients. But if the purpura is extensive, a course of cortisone, or preferably prednisolone, can be begun at once. Full doses should be used; for adults, 300 mg. a day of cortisone or 40 mg. a day of prednisolone in divided doses; for children, about 200 mg. of cortisone or 30 mg. of prednisolone daily are right. This course should be continued for four weeks, and the position then reviewed. There may have been a complete remission with disappearance of the purpura and a rise of the platelet count to normal levels; in these cases the treatment is stopped and the remission often proves to be permanent.

The patient should be seen at intervals for the next twelve months; if a relapse occurs, splenectomy should be carried out. More commonly the purpura disappears partially or completely, but the platelet count remains low. Steroid treatment should be continued for a further period, up to three months; if the platelet count remains below 40,000 per c.mm., splenectomy should be carefully considered, even though the purpura itself is now minimal. The reason for this is that with so low a platelet count, cerebral hæmorrhage and hæmorrhage elsewhere in the central nervous system is always a possibility. If at any time a patient shows signs of an incipient central nervous system hæmorrhage, splenectomy becomes urgently necessary. Splenectomy should also be considered early in girls approaching the time when the onset of menstruation is expected, and in the young married woman likely to become pregnant. Patients whose thrombocytopenic purpura has appeared during pregnancy have been successfully carried through, but no-one would willingly add this hazard if it could be avoided.

Acute thrombocytopenic purpura is fortunately rare, but is very alarming when it does occur. The patient gives a few days' history of extensive purpura, bleeding from nose and gums, and sometimes hæmaturia; vaginal hæmorrhages may be serious. The patient is very poorly and the hæmoglobin may be low. Once the diagnosis is established the best treatment is blood transfusion followed by prednisolone. Emergency splenectomy used to be recommended for this condition, but has mostly been abandoned because in so many patients the platelets failed to rise for some days, or weeks, after the operation, and then the complication of a bleeding abdominal wound was added to the clinical difficulties.

Present technique is to tide the patient over the acute crisis by transfusion and prednisolone and to carry out splenectomy in a quiet period later on, if the platelets do not rise spontaneously. In this type of case the question of platelet transfusion has to be considered. In blood collected and stored

in the usual way there are few platelets because so many have stuck to the glass, metal and rubber of the collecting apparatus. If all glass surfaces are siliconed, metal surfaces coated with a suitable water-repellent, and silicone rubber or plastic tubing is used for connexions, platelets can be kept intact and are available for transfusion. Transfused platelets survive for four to five days and might seem to be valuable for tiding the patient over an acute crisis. Unfortunately experience has shown that platelet antibodies develop very quickly in the recipient's blood, so that after the first transfusion the survival of platelets is so short that the effort is not worthwhile. There is evidence that 'platelet groups' exist, but no method of determining compatibility has been worked out.

Splenectomy is thus still the recommended treatment for all patients with thrombocytopenic purpura who have failed to show spontaneous remission and have not responded to a 3-month course of cortisone or prednisolone. Splenectomy is successful in most patients. In a group of 81 patients with primary thrombocytopenic purpura seen at Manchester Royal Infirmary, 64 had splenectomy carried out; 47 (74 per cent.) showed the expected rapid rise of platelets to normal, in another nine (14 per cent.) the platelets rose after a delay, so the operation achieved its object in 88 per cent. of patients. It would be satisfying if we could pick out beforehand the 12 per cent. who are the failures; this has proved difficult, but some progress is being made. Most of the failures are women over 45 years old, and it is clear that the chances of a successful response to splenectomy diminish sharply after that age. On histological examination of the spleen a very few have proved to have reticuloses, but such cases are not included in the figures given. Spontaneous recovery occurred in 10 out of these 81 patients (12 per cent.), and this rate is undoubtedly higher in children. So far there is no clear evidence that cortisone has raised the remission rate, but it is known that cortisone, possibly by influencing capillary fragility, has diminished actual bleeding and made splenectomy a relatively easy procedure free from complications.

For the treatment of thrombocytopenia caused by drugs, the object is to tide the patient over until depressed platelet production recovers or until platelet antibodies die away. Splenectomy is not part of the treatment for this group; blood transfusion and cortisone or prednisolone are used.

ANAPHYLACTOID PURPURA

This is the type often given the eponym 'Henoch-Schönlein purpura', and it is the most important non-thrombocytopenic purpura. The clinical picture presents a typical purpuric rash accompanied sometimes by joint swelling, and sometimes by evidence of alimentary-tract hæmorrhage. The rash is at first strikingly bright red and the affected areas are swollen; often the swelling precedes the coloration. The bright red soon changes to purple and then more slowly to brown. Since recurrent crops of purpuric spots

are a feature, most patients present all three stages at the same time. The patient complains that the affected area aches and is tender to the touch, and in the early stages there may be typical irritation at the site. Sometimes ecchymoses, varying from half-an-inch (12.5 mm.) across to large areas several inches across, occur and these are often notably painful. Dependent areas like the legs tend to show the most extensive rash, and pressure points are often marked out by spots. Bleeding from mucous membranes is unusual.

The blood count is always normal and the platelets are normal or slightly depressed. The bleeding time may be somewhat prolonged and the Hess test is sometimes positive. Negative pressure tests, such as that devised by Scarborough (1941), are always positive. In this test a standard negative pressure is applied to a defined area of skin on the forearm for a standard time, and the number of petechiæ that appear is counted; more than one or two indicates increased capillary fragility. The test is also positive in thrombocytopenic purpura.

Anaphylactoid purpura is commonest in children but is quite frequent in young adults; patients over 50 are rarely affected. In children it clears up quickly as a rule, but in adults it often becomes distressingly chronic. In young adults, too, this purpura is often the forerunner, by a few years perhaps, of renal disease and failure. For this reason the urine should always be examined microscopically for the presence of red cells, and renal function checked by carrying out a urea clearance test.

Diagnosis.—This is usually quite clear from the features of the rash and the absence of all changes in the blood count or in tests of blood clotting properties. There are only a few other conditions that need to be considered. The so-called 'senile purpura', which appears to be due to a loss of supporting substance in the subcutaneous tissues, shows fairly large and painless patchy lesions. In scurvy the lesions are also more than petechial and, if the skin is affected, the gums are likely to be affected as well; the skin shows follicular hyperkeratosis and not urticaria. Similarly in purpura accompanying infectious diseases, by the time the purpura appears, the diagnosis is already certain.

Etiology.—This type of purpura is often called 'allergic' purpura, but Ackroyd, in his review, points out that, apart from a few cases in which food allergy was definitely established, the cause of the syndrome is unknown and there is no good evidence for the implication of allergy. He points out that platelets and capillary endothelium are antigenically related. His extensive search into the nature of the purpura caused by 'sedormid' has shown that the thrombocytopenia is due to combination of the drug with platelets to form an antigen which in a few patients stimulates the production of a platelet-destroying antibody. The capillary lesion may also be produced when the drug combines with endothelial cells to form an antigen which reacts with this same antibody. Such a reaction may be the

cause of the non-thrombocytopenic purpuras and work along these lines is proceeding. At Manchester we have seen patients with purpura associated with the presence of an abnormal globulin in the serum and these cases are being investigated to see if they will help in solving this puzzle.

TREATMENT OF ANAPHYLACTOID PURPURA

Patients with Henoch-Schönlein purpura should be tested to see if any allergen, food or inhalant, can be implicated. In the few cases in which this search is rewarded, desensitization can be carried out.

If the urticarial element is prominent, the use of antihistamines is worth exploring: they will often cause the rash to clear, but may not prevent new crops of purpuric spots from appearing. 'Dibistin', a mixture of 50 mg. of antazoline and 25 mg. of tripeleennamine, has proved very useful in this purpura; one 75-mg. tablet is given three times daily. Promethazine, 25 mg. three times daily, has also helped in some patients.

The relief of patients by cortisone has been reported quite often in the literature. It is difficult to sort out the therapeutically induced from the spontaneous remission in individual cases, but the balance of evidence is in favour of its value. In my experience cortisone will produce remissions in some chronic cases. The dose should be 300 mg. a day at first, reducing to 200 mg. daily if signs of fluid retention appear. Nowadays, prednisolone is often used instead, the dose being 40 mg. daily at first, dropping to 30 mg. If a remission occurs the cortisone dosage should be dropped in steps to 50 mg. a day for about a month, and then stopped. If after one month's treatment a remission has not appeared, there is no point in continuing the treatment and the dose should be reduced in steps to zero.

Adrenochrome monosemicarbazone ('adrenoxyl') and related compounds have been said to reduce capillary fragility in animals and have therefore been tried in cases of Henoch-Schönlein purpura. In Manchester we have tried this substance, but the results have been disappointing.

Splenectomy should not be carried out in this type of purpura; it brings no relief. Sometimes the operation is followed by a phase of remission, but sooner or later the disease reappears.

Fortunately, in many patients the disease remits after a few weeks or months, but in others it keeps recurring with much pain and disability, and so far we have only symptomatic treatment to offer.

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HÆMOGLOBIN AND ITS ABNORMALITIES

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THIS article will concern itself with the changes in the nature of hæmoglobin. These do not necessarily cause an anæmia, but they are often of clinical importance, and some are of wider interest from the point of view of biochemistry, biophysics, physiology, genetics and even of anthropology.

THE HÆMOGLOBIN MOLECULE

Hæmoglobin is a conjugated protein in which the hæm, a ferroporphyrin, is the prosthetic group. Four hæms are attached to the protein moiety—globin. Hæmoglobin is by no means confined to the higher animals, or even to the animal kingdom. It has been found in protozoa, in the roots of leguminous plants, in yeasts and in moulds (Keilin, 1953). The hæm is identical in all species. The molecular weight of the globin varies in invertebrates, but in vertebrates it is uniformly 68,000. The nature of the globin, however, varies from animal to animal and is different in the multiple hæmoglobins of a single species.

CHANGES IN THE HÆM

The physiological function of hæmoglobin is based upon its loose combination with oxygen. Oxyhæmoglobin loses the oxygen when the partial pressure of the gas falls, and it becomes re-oxygenated when the oxygen pressure is restored. This reversible oxygenation does not involve the iron atoms which are in the divalent ferrous form. When the ferrous hæmoglobin becomes oxidized to ferric hæmoglobin—methæmoglobin—the curve of dissociation is changed. It becomes more difficult to exchange the loosely bound molecular oxygen. Similarly, if the ferrous hæmoglobin combines with carbon monoxide instead of with oxygen or carbon dioxide, carboxy-hæmoglobin results with a dissociation curve which does not allow reversible oxygenation to proceed easily.

Methæmoglobinæmia.—There is a steady formation of methæmoglobin in the red cells but enough reduced coenzyme I (diphosphopyridine nucleotide) is formed during glucolysis to reduce the ferric protein as rapidly as it is formed. Methæmoglobinæmia may occur as a result of the toxic effects of drugs such as phenacetin, acetanilide and antipyrin. In these cases the methæmoglobin disappears within a few days of withdrawing the drug. There is a rare condition—only a few dozen cases have been described—in which methæmoglobin is congenital and where it persists in the absence

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of specific treatment (see Barcroft *et al.*, 1945). The cause is an inherited deficiency of a flavoprotein (coenzyme factor I) which acts as a catalyst in the reduction of methæmoglobin by coenzyme I (Gibson, 1948).

Although methæmoglobinæmia may cause a marked cyanosis, most patients suffer from no physical disability. Methæmoglobinæmia should be suspected whenever there is a deep cyanosis without dyspnœa. In some of the congenital conditions, however, methæmoglobin may form nearly half of the red cell pigment, and there may be dyspnœa on effort. Treatment with ascorbic acid by mouth or by injection will reduce the cyanosis dramatically, and this can be used as a diagnostic test. Methylene blue given by mouth will act even more rapidly and completely. It couples the methæmoglobin with reducing enzymes which otherwise have no effect, or act only at a slow rate.

There has also been described one family with hereditary methæmoglobinæmia where the globin moiety was abnormal, and where treatment with methylene blue or with ascorbic acid failed to bring about a reduction of the ferric ion (Hörlein and Weber, 1948). On separation of the hæm and globin and recombination with those of normal persons it was possible to show that the globin of the members of the affected family was incapable of forming a ferrous protein.

Sulphæmoglobinæmia.—When methæmoglobinæmia is associated with prolonged or excessive ingestion of drugs, and particularly if there is also a history of constipation, varying proportions of the pigment will be further converted into sulphæmoglobin. In practice sulphæmoglobinæmia is the more frequently encountered condition. Sulphæmoglobin cannot be converted into normal hæmoglobin by reducing agents. Excessive putrefaction in the intestine can cause an increase in hydrogen sulphide, and it has been demonstrated experimentally that hydrogen sulphide can react with hæmoglobin in the presence of oxygen to form sulphæmoglobin, and that this process is accelerated when derivatives of aniline are present (Archer and Discombe, 1937). The exact nature of sulphæmoglobin is still unknown. Presumably a nitrogen bonded to the iron atom is replaced by sulphur. As in drug-induced methæmoglobinæmia, so in sulphæmoglobinæmia the treatment consists primarily in stoppage of the offending therapeutic agent, but it is also worth avoiding the accumulation of food residues in the colon.

ABNORMAL SYNTHESIS OF THE GLOBIN

In contrast to most of the conditions in which hæmoglobin is abnormal as a result of changes in the hæm, the known abnormalities of globin synthesis are all permanent and inherited. The diseases caused by such abnormalities have been called hæmoglobinopathies. They are characterized either by a block in the production of normal hæmoglobin or by its replacement by one of its variants, or by a combination of these two. All hæmoglobinopathies show an increased rate of hæmolysis. It is now known that a variation in hæmoglobin synthesis may not invariably cause a hæmoglobinopathy, particularly in heterozygotes for an abnormal gene. To include all conditions

it might be more appropriate to call them hæmoglobinoses (table I), some of which would then be hæmoglobinopathies.

	Hæmoglobin F	Other Hæmoglobins
<i>Sickle-cell anæmias (S.C.A.)</i> Classical S.C.A. Microdrepanocytic disease	Usually present Usually present	S S + A A may be absent S + C S + D
Hb. C S.C.A. Hb. D S.C.A.	Usually present Up to now always found	
<i>Thalassæmias (Thal)</i> Thal major (homozygous)	Can vary from nil to 90 per cent., usually 10 to 20 per cent.	A with raised proportion of A ₂
Thal minor (heterozygous)	Usually present, but more often absent than in Thal major. Rarely 10 per cent.	A with raised proportion of A ₂
Hb. C thalassæmia Hb. D thalassæmia (one case)	Present as in Thal minor 4 per cent.	C + A D + possibly trace of A
Hb. E thalassæmia Hb. H thalassæmia	20 to 40 per cent. Present	E A + H
<i>Non-sickling, non-thalassæmic diseases</i> Hb. C disease	Traces present, but not regularly	C
Hb. D disease (not proven by family studies)	Absent	D
Hb. E disease Hb. M disease	Absent or traces ?	E A + M?
<i>Conditions not known to give rise to diseases (traits)</i> Sickle-cell trait	Absent	A + S
Hb. C trait	Absent	A + C
Hb. D trait	Absent	A + D
Hb. E trait	Absent	A + E
Hb. G trait	Absent	A + G
Homozygous G (one case only)	Absent	G
Hb. H trait (presumed in parents of Hb. H thalassæmia)	Absent	A
Hb. I trait	Absent	A + I
Hb. J trait	Absent	J + A
Hb. K trait	Absent	A + K

TABLE I.—The Hæmoglobinoses.

The abnormalities of hæmoglobin synthesis can be divided into three groups:—

(1) Conditions in which there is an inherited defect in the production of normal hæmoglobin not associated with a deficiency of hæmopoietic substances. Thalassæmia is an example.

(2) Conditions in which normal hæmoglobin is replaced by one or two abnormal variants. Some of these variants have been proved to be allelomorphs of normal hæmoglobin. Sickle-cell anæmia is an example.

(3) Combinations of 1 and 2. Sick-cell thalassæmia (microdrepanocytic disease) is an example.

THE NORMAL HÆMOGLOBINS

The two physiological hæmoglobins are adult hæmoglobin (hæmoglobin A) and foetal hæmoglobin (hæmoglobin F). Both are under an independent genetical control (for an exhaustive review of hæmoglobin F see Betke, 1954). At birth more than half of the hæmoglobin is in the F form, its concentration falls steadily until, at the age of 4 to 6 months, none can be discovered by the usual chemical methods. Hæmoglobin F was discovered nearly a hundred years ago when it was noted that the red-cell pigment of the new-born infant, unlike that of the adult, was not denatured by alkaline reagents. To this day most laboratories measure the concentration of hæmoglobin F by determining the percentage of 'alkali-resistant hæmoglobin'.

The two hæmoglobins differ in their oxygen dissociation, the curve of hæmoglobin F being to the left of that for hæmoglobin A. In the ultra-violet spectrum the position of the tryptophane fine-structure band differs by 12 Å. There are slight differences in the isoelectric point, and hence in electrophoretic mobility, and also in immunological specificity.

Hæmoglobin F cannot be called an abnormal hæmoglobin but its presence after the age of 6 months indicates that there is some early impediment of hæmoglobin A production. The inherited hæmoglobinopathies begin to cause anæmia within a few months after birth, at a time when hæmoglobin F is still produced, and it seems that anæmia in early infancy is associated with a persistence of the foetal pigment beyond the age at which it is normally found. Thus, the finding of hæmoglobin F is almost a part of the diagnostic procedure for thalassæmia and sick-cell anæmia. The early anæmia associated with a persistence of hæmoglobin F need not necessarily be due to an intrinsic defect of hæmoglobin A formation (Singer *et al.*, 1951; Beaven and White, 1953; Chernoff, 1955). The phenomenon is seen occasionally in spherocytic anæmia where the abnormality is one of the red-cell shape leading to an increased elimination of red cells by the spleen, in leukæmia, in malnutrition, and even in cyanotic conditions such as congenital heart disease where there is only a relative lack of hæmoglobin and no anæmia.

THALASSÆMIA

In thalassæmia, also known as Cooley's anæmia, microcythæmia, Mediterranean anæmia and hereditary leptocytosis, there is interference with the expression of the gene responsible for hæmoglobin A formation. Although the term thalassæmia was introduced to indicate the frequency of the condition in Italians and Greeks, the gene is now known to occur in many different races. Thalassæmia was the first hæmoglobinopathy for which a familial incidence was established, and in which it was shown that the homozygotes were more severely affected (Angelini, 1937; Caminopetros, 1938; Gatto, 1941; Dameshek, 1943; Valentine and Neel, 1944).

Thalassæmia major.—The homozygous condition, thalassæmia major, results in severe anæmia; death usually intervenes before adolescence. The clinical picture and the laboratory findings show similarity with those seen in iron-deficiency anæmia. The cells are hypochromic and microcytic. There is much anisocytosis, and poikilocytes and target cells ('Mexican hat cells') are numerous. Nucleated red cells are present when the condition is severe. In contrast to iron-deficiency anæmia the microcytosis tends to be due more to flatness of the cells than to a decrease in their diameter. As the resistance of a cell to hydration is largely a measure of the difference between the volume of the red cell and that of a sphere of equal surface (Castle and Daland, 1937), it is not surprising that the flattened cells of thalassæmia show a greatly decreased osmotic fragility: some remain intact when suspended in distilled water. It is often difficult to distinguish thalassæmia from iron-deficiency anæmia; in both the defect is one of hæmoglobin synthesis rather than of cell maturation. Although there is an increased rate of hæmolysis in thalassæmia, serum bilirubin level is usually not raised. In iron-deficiency the hæmoglobin A formation is inhibited by the difficulty of finding enough iron to produce an adequate amount of hæm, hence the anæmia improves with iron therapy. In thalassæmia the materials for hæmoglobin A production are all present, but the erythroblast cannot make use of them. Iron therapy is useless, and there is the apparent paradox of a hypochromic microcytic anæmia with copious iron stores in the bone marrow and a high serum iron level. Fœtal hæmoglobin is almost invariably present—another difference from iron-deficiency anæmia (Liquori, 1951). There is no correlation between the amount of hæmoglobin F and the severity of the anæmia.

Thalassæmia minor.—The heterozygous thalassæmia is usually less severe than thalassæmia major. As a rule, interference with the gene responsible for hæmoglobin A formation is less marked, and the condition has therefore been called thalassæmia minor. In some instances only will the penetrance of the single thalassæmia gene be so powerful that the term 'minor' becomes a misnomer. Family studies may then be required to prove that the patient is not a homozygote. The majority of thalassæmia heterozygotes show some signs of abnormal hæmoglobin synthesis, but the anæmia is only moderate or may be entirely absent. The blood film shows hypochromia, poikilocytosis and leptocytosis, and the decrease in mean corpuscular thickness can either be measured directly or can be inferred from a raised resistance of the cells against lysis by hypotonic saline solutions. Some hæmoglobin F is usually present.

In some thalassæmics the penetrance of the single gene can be so poor and cause so little disturbance of hæmopoiesis that the abnormal genotype can only be ascertained from a family study.

The reason for the wide variation of penetrance is unknown. It has been suggested that there might exist different thalassæmia genes. There is no doubt that there are some notable differences between the blood picture of thalassæmia minor in Italy

and of the few instances of the condition seen recently in the Gold Coast (Edington and Lehmann, 1955). Widely differing degrees of severity may be seen in the thalassæmic offspring of the same parents.

Hæmoglobin A₂—the Kunkel phenomenon.—Careful analysis of normal hæmoglobin of adults has demonstrated that it consists of at least two, possibly three, fractions. One of them, hæmoglobin A₂, resembles in its electrophoretic mobility the abnormal hæmoglobin E (Kunkel and Wællenius, 1955). Normally not more than 3 per cent. of hæmoglobin A is in the A₂ form, but A₂ is present in concentrations up to 15 per cent. in a majority of thalassæmics. Examination for a raised proportion of hæmoglobin A₂ may become a useful tool in the diagnosis of thalassæmia.

In thalassæmia the amount of circulating hæmoglobin A is low because of the interference with the synthesis of the normal pigment. In the other hæmoglobinoses an abnormal variant replaces it to a varying extent.

THE SICKLE-CELL AND ITS HÆMOGLOBIN

The first variant of adult hæmoglobin to be discovered was the sickle-cell hæmoglobin (hæmoglobin S). It is of interest to note that forty years elapsed

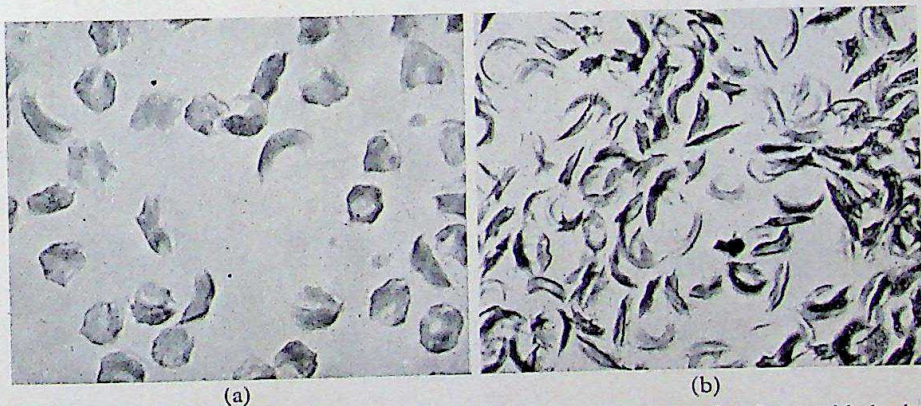


FIG. 1.—Sickle cells: (a) Sickle cells shortly after a reducing agent has been added; the early stages of sickling can be noted. ($\times 750$.)
(b) A preparation in which sickling is nearly complete. ($\times 500$.)

between Herrick's (1910) first description of 'peculiar elongated and sickle-shaped red corpuscles in a case of severe anæmia' (fig. 1) and the fundamental announcement by Pauling and his colleagues (1949) that sickle-cell anæmia was a molecular disease due to an abnormal hæmoglobin.

Most of the techniques which up to then had been employed to differentiate between the adult and foetal pigments would have failed to recognize the hæmoglobins discovered since 1949. Hæmoglobin F is so far unique in being resistant to alkali, in possessing a different ultra-violet spectrum and in showing immunological specificity. On the other hand, hæmoglobins A and F differ little on electrophoresis, and this was the technique by which hæmoglobin S was discovered (fig. 2).

In this technique proteins are dissolved in a buffer solution and an electric current is passed. The charge of the protein and the speed at which it will migrate towards the negative or the positive pole depend upon the difference between the pH of the buffer and the pH at which the protein is isoelectric. If both are the

same the protein will be neutral and remain stationary. If the pH of the buffer is on the acid (negative) side of the isoelectric point the protein will carry a positive charge and will move towards the cathode, and if the pH of the buffer is on the alkaline (positive) side, the protein will behave as an anion and move towards the anode.

The isoelectric points of hæmoglobins A and F are very similar (6.9 and 6.9 to 7 respectively), hence electrophoresis has not been an efficient method of separation. The isoelectric point of hæmoglobin S is 7.1, hence once electrophoresis was applied a separation was easily achieved.

The first sickle-cell anæmia patient seen was a West-Indian Negro who was in Chicago as a student. Subsequent observations were also made on

Negroes (fig. 3). It was then noted that some Negroes had erythrocytes which appeared perfectly normal *in vivo*, but which could be induced to sickle *in vitro*. Hahn and Gillespie (1927) reported that sickling only occurs with low oxygen tensions and that sickled cells revert to the normal shape when they are exposed to sufficient oxygen. A slightly acid pH seemed to favour sickling. The sickling phenomenon was found to be familial, and the mode of inheritance that of a single Mendelian dominant (Emmel, 1917; Taliaferro and Huck, 1923). At first it was assumed that the same gene produced in some persons an asymptomatic condition—the sickling trait, and in others was responsible for a severe disorder—sickle-cell anæmia. Neel suggested, in 1947, that there might be an alternative hypothesis similar to that which differentiated between thalassæmia major and thalassæmia minor as homozygous and heterozygous states. In 1949, he presented convincing evidence, and simultaneously and independently the same hypothesis

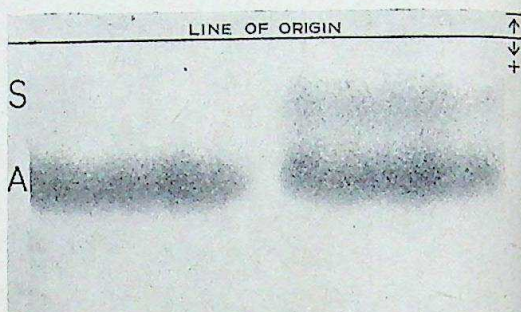


FIG. 2.—Comparison by paper electrophoresis (pH 8.6) of normal hæmoglobin (A) with that of sickle-cell trait carrier (A + S). The normal hæmoglobin moves as a single band, whereas the abnormal hæmoglobin separates into two components, one identical with A, and one moving more slowly—hæmoglobin S.

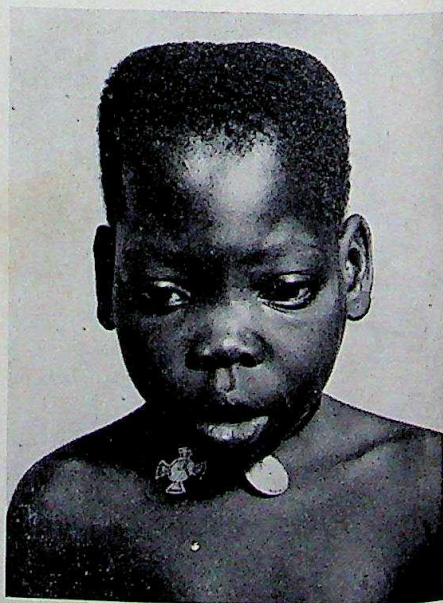


FIG. 3.—Photograph of child with sickle-cell anæmia. Note bossing of skull. (By courtesy of Dr. P. W. Hutton, Uganda.)

was advanced by Beet (1949). Dramatic support was given to the genetic theory when Pauling discovered the sickle-cell hæmoglobin, and when it was shown that patients with sickle-cell anæmia (homozygotes) had no normal hæmoglobin, but that sickle-cell trait carriers (heterozygotes) possessed both the abnormal and the normal pigment.

In most cases of sickle-cell anæmia not all the hæmoglobin is hæmoglobin S; traces of hæmoglobin F are present (Singer *et al.*, 1951), and the finding or the absence of hæmoglobin F in a sickler is of help when a diagnosis has to be made without electrophoresis.

Direct evidence for the physical base of the sickling process was obtained by solubility studies.

Harris (1950) found that the de-oxygenation of concentrated solutions of hæmoglobin S resulted in a semi-solid gel. Under the microscope, tactoids 1 to 15 μ long could be observed which were remarkably similar in shape to sickled cells. On re-oxygenation the tactoids disappeared but they formed again when the oxygen was removed. Perutz and his colleagues (1950, 1951) found that reduced hæmoglobin S was much less soluble than reduced hæmoglobin A. Oxygenated hæmoglobins A and S have the same solubility, but, whereas on de-oxygenation the solubility of hæmoglobin A falls by one half, that of hæmoglobin S is only 2 per cent. of the solubility of the oxygenated pigment (*see also* Itano, 1953). When cells containing sickle-cell hæmoglobin are reduced, intracellular tactoids are formed. These formations stretch the cell envelope and produce the bizarre shape of the sickle-cell.

There had already been fundamental clinical observations by Diggs and his colleagues (1933), by which the anæmia had been separated from the trait, and careful observations by Sherman (1940) had shown that the two conditions differed in their tendency to form sickle cells. Sickle-cell anæmia is hæmolytic in nature with a reduction in survival time of the erythrocytes to two to eight weeks instead of the normal life span of six months. Trait cells survive normally even when they are transfused into a sickle-cell anæmia patient (Singer *et al.*, 1948; Callender *et al.*, 1949). All these observations can now be explained on the basis of the abnormal hæmoglobin content of the erythrocytes. The greater the tendency to sickle the more likely are hæmolytic crises to arise, and the more often will be seen the infarctive conditions which are typical for sickle-cell anæmia. As intravascular sickling may cause blockage of small vessels in all parts of the body, sickle-cell anæmia can present as a hæmaturia or as an acute abdominal emergency, as pneumonia, heart disease or with neurological manifestations. Arthralgia is frequent, and leg ulcers are common; these, however, are also a feature of the non-infarctive thalassæmia major and of hereditary spherocytosis. Harris and his colleagues (1956) have explained all the features of sickle-cell anæmia on a biophysical basis: 'The sickled erythrocyte is essentially a membrane-covered tactoid'. Because of the abnormal shape of the red cells there is an increase in the viscosity of the blood, and stasis results. The fall in pH and the continued uptake of oxygen by the tissues will cause more sickling. With a greater number of sickled cells the viscosity will increase further and the stasis will be prolonged. Sickled cells are more fragile than cells of normal configuration and when the erythrocytes are

released after stasis, a certain proportion have been fixed in the sickled form and have therefore become more fragile. Thus the abnormalities of the erythrocytes are responsible not only for the various occlusive conditions and venous thromboses that underlie the tissue changes but also for the hæmolytic anæmia.

Whether the heterozygous condition is always symptomless has been doubted. Splenic infarction associated with high-altitude flying has repeatedly been reported in non-anæmic sicklers. Conn (1954) has recently summarized nine instances in five of which the hæmoglobin level was above 14 g. per cent. There are numerous other examples which have not been published. Severe unexplained hæmaturia has been seen in a number of patients in whom the sickling condition was proved to be the trait (Goodwin *et al.*, 1950; Chernoff, 1955).

Keitel *et al.* (1956) have found that sickle-cell anæmia patients above the age of 7 years are unable to produce urine with a concentration above 500 milliosmol. Younger patients or adult patients who have been transfused with normal blood may concentrate their urine above this level. Of 26 sickle-cell trait carriers only eight achieved a urine concentration within the 95 per cent. range of normal. These authors suggest that this hyposthenuria results either from renal damage due to intravascular sickling—the kidney uses a great deal of oxygen—or that sickle-cell hæmoglobin interferes with the tubular function. It can be assumed that hæmoglobin S, like normal hæmoglobin, is reabsorbed by the tubular cells from the tubular urine. If the hyposthenuria of sicklers was caused by an effect of hæmoglobin S on the tubules a hitherto unknown process would have to be invoked. Simple intracellular precipitation of hæmoglobin S is unlikely at dilutions which must be well under 1 per cent.

NON-SICKLING HÆMOGLOBIN VARIANTS

On the whole, the recognition of hæmoglobin S, the studies of its biochemical and physical properties, and the examination of individual patients and their families went far to support the genetical theory which postulated that sickle-cell anæmia was the disease of the homozygote. Departures from this hypothesis led to the discovery of other abnormal hæmoglobins. For an exhaustive description the reader will turn with advantage to the following review articles: Singer, 1955; Chernoff, 1955; Zuelzer *et al.*, 1956; Itano *et al.*, 1956; Lie-Injo Luan Eng, 1956.

In addition to normal adult, foetal and sickle-cell hæmoglobin, nine other human hæmoglobins have been recognized up to date. In 1953, a group of interested workers was called together by the United States Public Health Service to meet under the chairmanship of J. V. Neel and to decide on a standard system of nomenclature. The following system was proposed and has been universally accepted ('Statement', 1953):—

Normal adult hæmoglobin: hæmoglobin A

Foetal hæmoglobin: hæmoglobin F

Sickle-cell hæmoglobin: hæmoglobin S

All other hæmoglobins were to be assigned letters of the alphabet in the order of their discovery beginning with the letter C (as B had at one time been used for sickle-cell hæmoglobin), unless as in the case of the first

three hæmoglobins there was some characteristic feature which would serve as a convenient mental association. Thus, Singer (1955) proposed later the letter M for the abnormal methæmoglobin of Hörlein and Weber (1948).

In following the alphabetical sequence the letters F and S would of course be omitted and the same should apply to any other letters which had already been used for reasons of alliteration.

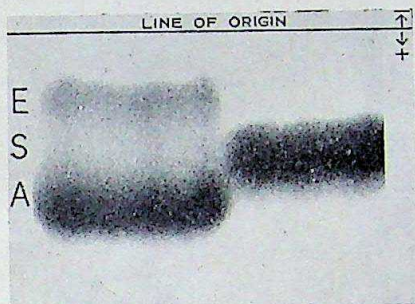


FIG. 4.—Comparison by paper electrophoresis (pH 8.6) of the hæmoglobin of a patient with sickle-cell anaemia, with that of a hæmoglobin E trait carrier. Note that at pH 8.6 S moves more slowly than A and faster than E.

HÆMOGLOBINS

C, D, E, G, H, I, J, K, M

Not all the nine non-sickling hæmoglobin variants have been examined with the same thoroughness, and indeed K and M are not yet well defined at the time this article is being written. Homozygotes have been described for C, D, E and G, but the essential proof of homozygosity by extensive family

studies is incontrovertible only for hæmoglobin C. For D it is presumed from the hæmatological and electrophoretic findings in a few individuals and, although a number of persons have been described in whom there was a strong presumption of homozygosity, so far in only two cases have both parents been examined and been found to be in the possession of hæmoglobins A and E (Lie-Injo Luan Eng, 1956; Brumpt *et al.*, 1956). In the case of G the homozygous state is presumed from the examination of a man's red cells which contained hæmoglobin G only, and from the finding

of the very rare variant in 10 of his 11 children. The one non-conforming offspring was a sickler in contrast to both his 'father' and his mother. Only preliminary data are as yet published on hæmoglobin K, and the mode of inheritance is not yet fully clarified for hæmoglobin H, but the other hæmoglobins all seem to be inherited

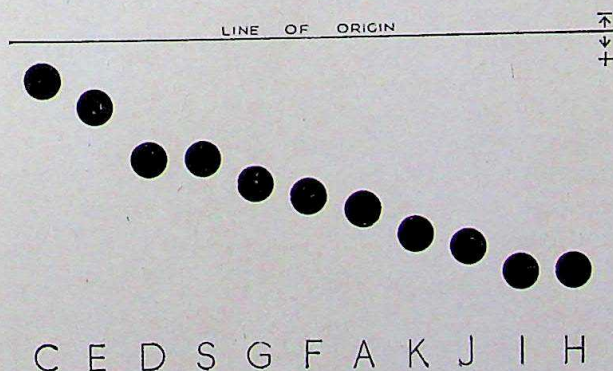


FIG. 5.—Scheme of mobility of the varieties of human hæmoglobin on electrophoresis at pH 8.6.

as simple Mendelian characters. Although it is likely that all the variants of adult hæmoglobin are allelomorphs, proof for this assumption has been provided only for hæmoglobins A, S and C (Ranney, 1954).

Hæmoglobins A, S, C, D, E, G, H, J and I have all been found to show no difference in their visible and ultra-violet spectrum, or in their resistance to alkaline denaturation.

The most important differences between the hæmoglobins from the laboratory point of view are in their behaviour on electrophoresis (fig. 4).

In 1953, Spaet showed that hæmoglobin variants could be separated by filter paper electrophoresis. Starch plates can be used instead of filter paper (Kunkel and Wallenius, 1955).

Paper electrophoresis is usually carried out at pH 8.6 and at this pH good resolution is achieved for most mixtures (fig. 5). Hæmoglobins S and D have identical electrophoretic properties and cannot be told apart by this technique. Reduced hæmoglobin D, however, is not as insoluble as reduced hæmoglobin S, hence it does not cause sickling. A sickle-cell test on the intact cells and the measurement of the solubility of the de-oxygenated form will distinguish between the two hæmoglobins. There is some difficulty in differentiating at pH 8.6 between hæmoglobins C and E, J and K, and H and I respectively. Further examination at pH 6.5 then becomes necessary. At that pH hæmoglobin C has the greatest mobility, but E is found between the positions of A and S. At pH 6.5 hæmoglobin H is still an anion and, unlike all the other hæmoglobins, will move towards the positive pole. Hæmoglobin K moves just a little more slowly than hæmoglobin J at pH 8.6, and a little faster than K at pH 6.5.

TRAITS AND DISEASES

Except for an occasional nephropathy or splenic infarct noted in AS heterozygotes, no abnormalities have been recorded in people heterozygous for hæmoglobin A and one of its variants—unless they carry in addition a gene for thalassæmia. The most severely pathological condition is the SS state. Hæmoglobin C disease, hæmoglobin D disease and hæmoglobin E disease are much less serious and seem usually to be compatible with a survival into adult life. No abnormality was noted in the one homozygote for hæmoglobin G who has so far been examined. The disease states are associated with an increased rate of hæmolysis. Whether this will result in anæmia, and whether this anæmia will be moderate or severe, will depend upon the degree of compensation achieved by a higher activity of the bone marrow. Target cells (fig. 6) are commonly seen in the hæmoglobinopathies and the osmotic fragility is decreased. They all show a resemblance to thalassæmia, but an analysis of the hæmoglobin will differentiate the various syndromes.

Schwartz and Hartz (1955) have re-examined families in whom, in 1949, a diagnosis of thalassæmia had been made on clinical grounds and because of the thalassæmia-like appearance of the blood smear. They found that in some of the patients the underlying cause of the hæmoglobinopathy was in fact hæmoglobin C and not thalassæmia.

Two conditions are known in which there is heterozygosis for two

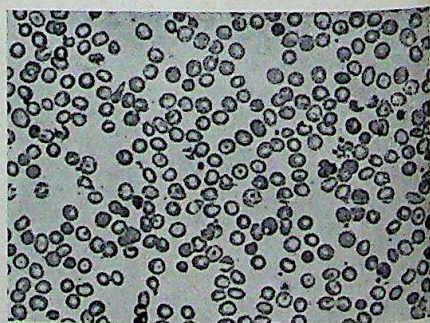


FIG. 6.—The characteristic feature of the non-sickling hæmoglobinopathies is a high proportion of target cells. ($\times 250$.)

abnormal hæmoglobins: hæmoglobin C—sickle-cell anæmia (SC), and hæmoglobin D—sickle-cell anæmia (SD). In each case an atypical course of sickle-cell anæmia led to their discovery. The clinical state is most variable. Completely asymptomatic 'patients' have been described who would have been unnoticed had not the relatives of a more affected person been examined. On the other hand, there may be serious debility comparable in severity to homozygous sickle-cell anæmia. In addition, whereas sickle-cell anæmia does not show much fluctuation of severity, except for the occasional crises, SC disease at least, and to a lesser extent SD disease, may vary considerably in their symptoms when the same patient is seen at intervals. Homozygous sickle-cell anæmia usually causes early death; a heterozygous condition should therefore be suspected when an adult person suffers from sickle-cell anæmia.

COMBINATION OF ABNORMAL HÆMOGLOBIN WITH THALASSÆMIA

Before the abnormal hæmoglobins had been discovered an important observation had been made by Silvestroni and Bianco (1955). They had noted that in some patients both sickling and thalassæmia contributed to the blood picture of patients suffering from a condition which was otherwise indistinguishable from sickle-cell anæmia. They named the syndrome microdrepanocytic disease (microcythæmia plus drepanocytosis). Examination of families in which one parent of a child with sickle-cell anæmia failed to sickle led to the discovery of microdrepanocytic disease with increasing frequency. The usual mode of inheritance is that one parent contributes a thalassæmia gene, and the other a gene for hæmoglobin S. But as the two factors are under an independent genetical control, it is possible for a parent with microdrepanocytic disease to transmit both abnormalities. As the thalassæmia gene causes a blockage in the synthesis of hæmoglobin A, the patient, though heterozygous for hæmoglobins A and S, will possess a greater proportion of the abnormal hæmoglobin than is found in the non-thalassæmic sickle-cell trait carrier. Hæmoglobin F is usually present, but as it is also found in homozygous sickle-cell anæmia its demonstration cannot contribute to the diagnosis. The majority of patients with microdrepanocytic disease present with a moderately severe sickle-cell anæmia, but there is a variability in the condition resembling that seen in thalassæmia minor. The penetrance of the thalassæmia gene may range from nil to one resulting in complete suppression of hæmoglobin A production. In the extreme cases family studies are required to differentiate the microdrepanocytic condition from sickle-cell trait or from sickle-cell anæmia.

Thalassæmia has also been seen in combination with hæmoglobins C, D, E and H.

Hæmoglobin E thalassæmia is often found in South-East Asia, although it was first discovered in a half East Indian child in the United States (Itano *et al.*, 1956).

The most important studies were made in Siam (Chernoff, 1955) and subsequent observations were made in Indonesia, Burma, and Bengal. In hæmoglobin E thalassæmia no hæmoglobin A is found, and its place is taken by 20 to 40 per cent. of hæmoglobin F. Complete absence of hæmoglobin A has also been noted in some patients with hæmoglobin C thalassæmia, and the one patient with hæmoglobin D thalassæmia so far described showed no hæmoglobin A on paper electrophoresis, but zone electrophoresis revealed a trace (Hynes and Lehmann, 1956).

A somewhat complicated chain of inhibition of gene penetrance seems to exist in the case of hæmoglobin H (Motulsky, 1956). All the AH phenotypes seen so far were double-heterozygotes for thalassæmia and hæmoglobins A and H respectively. Where family studies have been possible it has always been found that one of the parents of the propositus was a heterozygote for thalassæmia, but that neither parent possessed the abnormal hæmoglobin. The available evidence suggests that the gene for hæmoglobin H shows no penetrance in the AH heterozygote unless there is a partial block of hæmoglobin A synthesis by thalassæmia.

RACIAL DIFFERENCES IN THE DISTRIBUTION OF THE HÆMOGLOBINOSES

The frequencies of the genes for thalassæmia and for the abnormal hæmoglobins differ among the human races (fig. 7) (Lehmann, 1954, 1956). When sickling was first discovered the phenomenon seemed to be restricted to Negroes. A few 'white' sicklers were found, but Negro ancestry could not be ruled out. As one might expect the sickle-cell gene is present in tropical Africa, but it is not equally distributed among the African races. The highest incidences occur in that part of the continent which lies south of the Sahara desert and north of the Zambesi river. Even within this tropical belt some races such as the Hamitomorphs of East Africa are virtually free from sickle cells. Sickling is found occasionally in Mediterranean populations where one might assume that the gene has been imported with African slaves in Roman times. A recent introduction by Turkish soldiers seems to be established for Thrace. In the Middle East, sickling is found in a number of Arab communities; some genes have undoubtedly been introduced with East African slaves, but it is possible that others have been inherited from the pre-semitic populations of Arabia. Of special interest is the presence of sickling in some Veddoïd tribes of Southern India. The Dravidian and Aryan populations there show no sickle cells, and it has been suggested that Africa and India received the gene from the same source—the Middle East. It is from there that it is assumed that Veddoïd populations moved in prehistoric times southwards both into Africa and into India.

Hæmoglobin C is present at high frequency in West Africa, and within West Africa the highest incidences have been noted for the Northern Gold Coast. Hæmoglobin D has been found in 3 per cent. of North-West Indians, and in about 1 per cent. of Gujeratis who derive from the region of Bombay. Numerous other Indian populations have been examined but so far the only other finding is that of hæmoglobin E at low frequency, in Bengalis. Hæmoglobin E is present at a frequency of more than 10 per cent. in Burmese, Siamese and Eastern Malaysians. In Western Malaya, E is less often found, presumably because of the admixture of Indonesian immigrants who have come across the Straits of Malacca. Hæmoglobin E has also been found at

lower frequencies in Indonesia, Sarawak, Cambodia, and in Bengal and Ceylon, although in Ceylon it was present only in the aboriginal Veddas and not in the Singhalese.

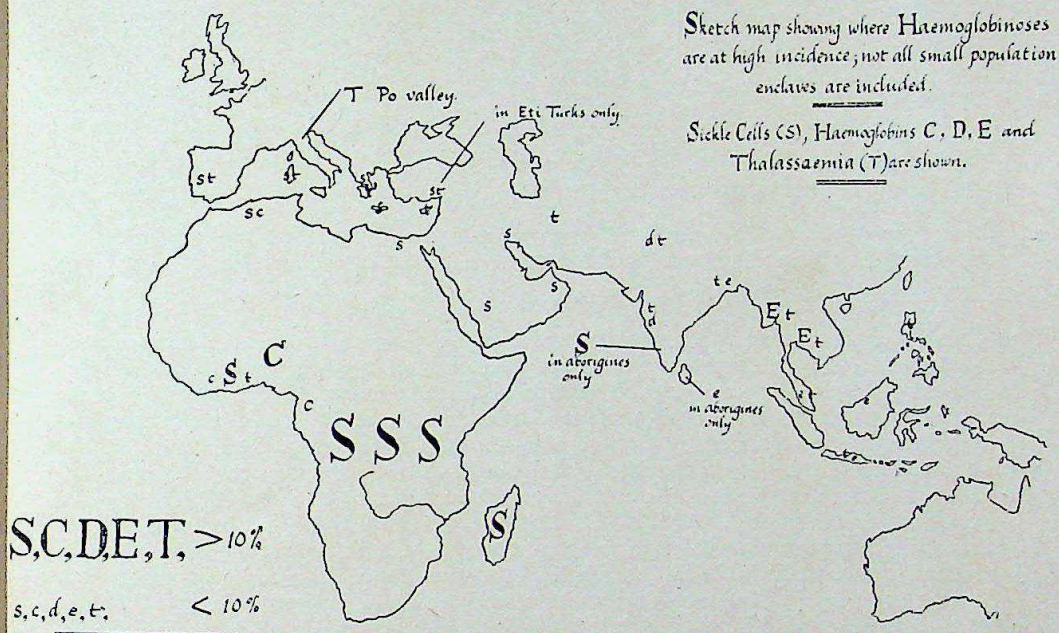


FIG. 7.—Sketch map showing world distribution of hæmoglobinoses.

The other hæmoglobins have so far not been found at regular frequencies but it seems that G, J, and K may exist at low incidence in West Africa, and although H was found in one Greek family and in one Arab from the Jordan, the other observations were made on Chinese, Filipinos and on one Malay.

Of all the abnormalities of hæmoglobin synthesis thalassæmia shows the most widespread distribution. At first discovered in Southern Europeans—and therefore called thalassæmia or Mediterranean anæmia—it has by now been found not only in nearly all the countries bordering on the Mediterranean but also in the Middle East, Pakistan, India, Burma, Thailand, Malaya, Indonesia, the Philippines and Cambodia. The condition has also been seen, though only occasionally, in Chinese and in American Negroes. A few instances have been seen in tropical Africa, and in Central and Western Europe.

SICKLING AND MALARIA

Many genes for thalassæmia and for abnormal hæmoglobins must be lost in every generation when hæmoglobinopathies cause death before the age of puberty. In particular, children with homozygous sickle-cell anæmia or with thalassæmia major rarely survive to become adults, and even then it is unlikely that they can have children. A successful outcome of pregnancy is

virtually unknown in these conditions. Yet in spite of their selective disadvantage, the genes responsible for the hæmoglobinopathies are at high frequencies in many parts of the world. Although a racially determined increase in the mutation rate for these genes has been envisaged, no support for this hypothesis could be found when families were examined on a large scale (Vandepitte *et al.*, 1955). An alternative explanation is a balanced polymorphism, where heterozygotes for the normal and the abnormal genes are more viable than both homozygotes (Neel, 1953). That the advantage for the heterozygote might be a greater resistance to malaria was a hypothesis adumbrated for sickling by Beet (1946), but was stated clearly first by Haldane (1949) who used thalassæmia as his example. A good deal has been written about the relation between sickling and malaria, much of it controversial (Edington and Lehmann, 1956).

The postulate is that AS heterozygotes die less often from malaria than normal homozygotes (AA). The proportionally greater loss of A genes would then balance the loss of S genes from sickle-cell anæmia. The AS heterozygote would possess enough hæmoglobin S to make his red cells unpalatable to the malaria parasite which is highly specialized in its metabolism to utilize hæmoglobin A, but on the other hand the hæmoglobin S content of the cells will be too low to cause sickle-cell anæmia. By directing attention to *P. falciparum* rather than to the malarial parasites in general Allison (1954) provided a sound experimental basis for further investigations. He was the first to produce concrete evidence in favour of protection of sicklers against malaria. This particular evidence could not be confirmed, but Allison's conclusions have been fully vindicated by Raper (1955, 1956), who found that there was no difference in the parasite rate between sicklers and non-sicklers, but that sicklers once infected showed a significantly lower density of *P. falciparum* in their blood smears. This applied only to children under the age of 2: i.e. before acquired immunity became established. After that age this secondary immunity protects sickler and non-sickler alike. As the severity of *P. falciparum* infection determines the malarial death rate of children in an endemic area, however, we have here the evidence supporting this first example of balanced polymorphism in man.

There may well be other advantages conferred by the hæmoglobinoses. It is noteworthy that some thalassæmics and some people whose hæmoglobin consists entirely of E or D have a blood picture resembling that of compensated iron deficiency. It is possible that such people can adapt themselves more easily than others to a diet deficient in iron or to loss of iron by chronic hæmorrhage due to hookworms. The most convincing evidence so far, however, relates to interaction with malaria.

Although not all populations living in malarious regions show an abnormality of hæmoglobin synthesis in some of their members, hæmoglobinoses have only been found at an appreciable frequency where malaria is also present. This is particularly notable in Africa where the Highlands of Kenya are free from sickling. Indeed, there have been attempts to deny an anthropological significance of the distribution of the hæmoglobinoses altogether, and to relate their presence or absence entirely to the selective advantage they confer or might confer on a malarious population. A glance at the map (fig. 7) will show that this is too extreme a view (*see also* Haldane, 1956). Nevertheless, it is remarkable that in contrast to many other primitive

aboriginal populations the Australians are free from hæmoglobinoses—malaria was not introduced into Australia until a few generations ago.

INCREASING IMPORTANCE OF THE HÆMOGLOBINOSES

Malnutrition and infectious diseases are on the decline in many countries where hæmoglobinoses are frequent. On the other hand, we know of no effective therapy and can use only palliative measures when we are confronted with a hæmoglobinopathy. It must be expected that the disorders of hæmoglobin synthesis will become increasingly important in many parts of the world. In the Lake Kopias area of Greece, where sickling and thalassæmia are frequent but where the once formidable malaria has now been eradicated, the hæmoglobinopathies are now the most pressing medical problem. It has been calculated that in the Commonwealth countries of West Africa alone three of every hundred children born should suffer from a hæmoglobinopathy. Whilst the over-all wastage of life before puberty was high this percentage was insignificant, but the higher the standard of public hygiene and the greater the improvements in nutrition the more significant will be this figure. In Italy marriage advice bureaus have been introduced in areas where thalassæmia is frequent. With an increasing standard of education and with a greater insight into the genetics of the hæmoglobinopathies similar services will be required in the African territories.

The hæmoglobinoses are also of medico-legal importance. I was present in Africa when two men claimed to be the father of the same child—a girl who would later bring in a valuable bride price. The problem was quickly settled by the pathologist when he found that the infant, but not her mother, was a sickler, and that of the two contestants only one was a sickler only. Hæmoglobin as well as the blood groups may be of more than theoretical interest when blood transfusions are given. Edington (1956) has described a post-mortem examination on an anæmic woman from the Gold Coast—a non-sickler—who had been transfused with two pints of AC and one of SC blood. The spleen was enlarged, grossly congested and in its histology not unlike the spleen seen in sickle-cell crisis. It was thought possible that the transfusion of the SC blood had been contributory to this woman's death.

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TONSILS AND ADENOIDS: EVALUATION OF REMOVAL IN 50 DOCTORS' CHILDREN

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It is practically impossible to absorb all that has been written about tonsils and adenoids and the results of their removal. It seems that an unusually accurate assessment, so far as children are concerned, might be made by studying the result of the operation upon doctors' own children, for there would be the great benefit of skilled observation of the illnesses for which the operation was undertaken and the results achieved. This analysis has been made upon 50 consecutive operations on doctors' children which I have performed in the last ten years or so, the parents having replied to a circular letter setting out the child's medical history before operation, asking for the effect on each symptom, for a general comment and ending with this sentence—'I know you will realize that I want a true report, even if it shows that the operation did not have all the good effects for which we hoped'. The series has the further advantages that the case histories and clinical examinations were made by one individual, who also performed all the operations according to a dissection technique evolved by three generations of surgeons at The Hospital for Sick Children, Great Ormond Street, where the indications for, and technique of, the operation have had serious and careful study for fifty years.

SCOPE OF INVESTIGATION

The indications for the operation were those accepted as a result of the accumulated experience of the medical and surgical staff of a large children's hospital, for the wise policy at that hospital has been that any member of the consultant medical or surgical staff may decide upon the operation; thus the specialist surgeon has a wide over-all knowledge of current opinion among pædiatricians, which is observed to change with changing years.

The case histories and doctor-parents' comments upon them and upon the results of the operation make up a large table, and since the object here is to present, in an easily assimilable form, an analysis of a highly selected small series, it seems best to discuss each symptom and its frequency and the result of the operation upon it in a separate paragraph. The paragraphs are arranged in order of frequency of symptoms, but it will be understood that many of the children had several of the symptoms and some of them all, and also that such a limited series does not display all the indications

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for the operation. No mention is made of the size of the tonsils and adenoids, although size of adenoids is inferred in nasal obstruction relieved by their removal. This is because the decision for the operation is based chiefly upon a careful history, and only in a minor way upon the size and appearance of the tonsils and adenoids, with some rare and rather startling exceptions which would not happen in taking the history from a doctor-parent. Tonsils and adenoids of an individual child vary in size and appearance in a most remarkable way, so that a description of their physical characteristics is only of value if based on repeated observation. In 1909, George Waugh stated that it is the 'septicity' of the tonsils and not their size which matters.

There is no example in the series of recurrent mesenteric adenitis dependent upon swallowed infection from bad tonsils; no example of tuberculous cervical adenitis; no case of rheumatism or nephritis; no child with insomnia and night-terrors and bed-wetting. But all of these may be definite indications that the tonsils and adenoids should be removed. Nor is there an example of prolonged poor health due to toxic absorption from the tonsils and adenoids, without a diagnosis of the source of the trouble having been made. Such 'sub-clinical' chronic tonsil infection is not uncommon in children's practice, but a doctor-parent would have noticed repeated redness of the throat and persistent enlargement of the tonsillar cervical glands, and probably a slight rise of evening temperature when his child was particularly off colour. It is in such children that the result of removal of the tonsils and adenoids is so often followed by a dramatic improvement in general health and growth.

Years ago it was the size of the tonsils and adenoids which condemned them; more recently the tonsils have been regarded chiefly from the point of view of sepsis and as foci of infection, whereas the size of adenoids is still a major consideration. Now we try to balance up the harm they are doing against the good they may still do as defensive and immunizing centres, and we remember that in the best circumstances it is a very safe operation.

Only children who had their tonsils and adenoids removed are included in the series. Often adenoids alone are removed when the symptoms are mainly attributable to them; or because it is thought wiser, in the first few years of life, to give the tonsils the benefit of any doubt so that they may continue to exert their immunizing function; or in the hope that resumption of nose-breathing when the adenoid obstruction is relieved will give the tonsils an opportunity to recover their condition. This hope is often doomed to disappointment.

There is no rigid age barrier and no insurmountable difficulty in the operative technique in the young child; but it seems right to demand more life for they have had such a short time to exert their ordinary function and to establish that their disease is beyond reasonable hope of spontaneous recovery.

TONSILS AND ADENOIDS

The youngest child was 2 years old and the oldest 15 years, the average age being five years and seven months. There were 30 boys and 20 girls, and the children were presented at a fairly even rate during the ten years. At the beginning of that period spring and summer were the times of election for the operation, but later on the control of common infections, particularly streptococcal, by chemotherapy or antibiotics robbed the winter of its chief drawback, and more recently the incidence of poliomyelitis in late summer has made the early spring the time of choice. It is also then that a succession of upper respiratory troubles stimulates the parents and doctors to take definite action to overcome them.

TONSILLITIS AND INFLAMED THROAT

Number of children 42. Cured 20. Improved 19. No change 3.

The most common complaint of the parents of the 50 children was of inflammation in the throat; half were called tonsillitis and half red throats with temperature. It is perhaps in the diagnosis of this that the greatest value was reaped from the parents being doctors, for it is well known that children seldom complain of a sore throat, and examination of the throat is often the only means of establishing the cause of a febrile illness. As might be expected the rate of cure of this condition was high, because how can a child with no tonsils get tonsillitis? It is often stated, however, that after tonsillectomy children continue to suffer from inflammation in the throat—pharyngitis instead of tonsillitis. This finds no support in this series because, apart from the 20 who had no more sore throats, 19 had fewer sore throats, mostly far fewer, and only three remained as susceptible to them as before operation.

OTITIS MEDIA AND DEAFNESS

Number of children 35. Cured 23. Improved 8. No change 3.

Onset after operation 1.

With these doctor-parents the occurrence of otitis media, amongst other troubles in the nose and throat, was often the factor which stimulated them to seek surgical advice. Their belief that ear infection often comes from infection in the tonsils and adenoids, chiefly the adenoids, is confirmed by the results of having them removed in their own children. Of 35 with otitis media 23 of the children had no more troubles, and only three were not improved. One child who had not had otitis media before operation has had several mild attacks during the four years which have elapsed since. Included in these numbers are three children who had had recurrent deafness without any pain or obvious inflammation in the ears; two of them had no more deafness, and one was said to be perhaps a little deaf still, but there had been no recent test.

CERVICAL GLAND ENLARGEMENT

Number of children 33. Cured 21. Improved 9. No change 3.

None of the patients was presented only because there were enlarged

cervical glands, but in a number of them such glands had rightly made the parents suspect infection in the lymphoid tissue in the nasopharynx. Enlargement of the tonsillar gland is a valuable sign of tonsil sepsis and it is remarkable how seldom other foci of infection in the mouth and throat affect this gland, except indirectly through the tonsil; indeed if it is found to remain enlarged after tonsillectomy experience leads one to suspect an infected tonsil remnant, or tuberculosis. Septic absorption from the nasopharynx causes enlargement of a number of superficial glands in the posterior triangle of the neck, the most usual combination of causes being post-nasal discharge from naso-sinusitis in a child whose adenoids have not been removed, or who has adenoid remnants. Although there was no example of tuberculous glands in this series such a condition certainly demands the removal of the tonsils and adenoids since they are the portal of entry of the tubercle bacillus. Of the 33 children who had enlarged cervical glands, in only three was there no marked improvement following the operation; the comments of their doctor-parents being: 'still palpable'; 'variable with infection'; and 'a few small, shotty cervical glands still present'.

COLDS

Number of children 26. Cured 0. Improved 20. No change 5. Worse 1.

The separation of this complaint from the two subsequent ones of nasal obstruction and nasal discharge is difficult and perhaps arbitrary. None of the doctor-parents brought their children just because of ordinary colds, but because they had found the colds unusually frequent and severe, often with pyrexia and red throat, or because they were accompanied by persistent nasal obstruction and discharge. One has always felt that it was too much to expect of a surgical procedure that it could prevent colds, the actual cause of which, probably a virus infection, still eludes us, but for many years I have had the impression that a child subject to severe colds is benefited in this respect by the tonsil and adenoid operation. This impression dates back some fifteen years when my two daughters had their tonsils and adenoids removed. But the number of doctors in this series who had the same experience was satisfying: 20 out of 26 children who had suffered severely from colds were reported by their parents to be greatly improved, and in only five was there thought to be no change.

The explanation may be that during a cold the infection lurks about in the irregularities on the surface and in the crypts of the tonsils, which are highly absorbing structures with profuse lymphatic drainage which carries the virus toxins into the blood stream causing a febrile illness. The cold also causes swelling of the adenoids which then obstruct the nasal passages so that they are not readily cleared. Muco-pus lying in the nasal cavities keeps up the inflammation of the underlying mucosa and its weight and sticky consistency prevent the action of the cilia. There can be little doubt that a properly cleaned nose recovers from a cold much more quickly than a neglected one, or one in which the discharge is sniffed back into the

nasopharynx and on to the adenoids. Colds in babies are difficult to manage because the baby readily adopts mouth-breathing and cannot blow his nose. The toddler may instigate swelling and growth of his adenoids by sniffing infected discharge backwards. The well-brought-up child saves his adenoids by blowing his nose properly, and his tonsils by eschewing mouth-breathing, and the infant may be helped to overcome a cold by sucking the discharge out of the nose with an all-rubber rat-tailed syringe. But if there is a failure and the tonsils and adenoids enlarge and become infected their removal seems very beneficial to colds in respect of their frequency, severity and duration. The one child in the series who had more severe, but not more frequent, colds suffered a bad nasal and sinus infection a month after operation.

NASAL OBSTRUCTION

Number of children 22. Cured 11. Improved 11.

The majority of these children had colds accompanied by severe nasal obstruction and continued to have a blocked nose between colds. The result of the operation was that half of them were cured, and the other half improved only, perhaps because they had never completely overcome their mouth-breathing habits, and suffered from recurrent congestion of their nasal mucosa. More rigorous breathing exercises were probably indicated. Of seven children who had nasal obstruction without excessive colds, six were cured, and one was reported as only improved.

NASAL DISCHARGE

Number of children 19. Cured 9. Improved 9. Worse 1.

It has been mentioned in the paragraph about colds that excessive nasal discharge may occur during colds because the child is unable to clean his nose properly due to swelling of the adenoids. If the adenoids remain swollen between colds the nasal air-currents are not able to maintain that freedom which is essential for the health of the nasal mucosa and it becomes congested and catarrhal, continuing to secrete excess of mucus or mucopus. The child has persistent nasal discharge which can, judging from this series, be improved or cured by removal of the adenoids. There is one exception, the child who developed nasal sinusitis during convalescence.

CHEST INFECTIONS AND COUGH

Number of children 10. Cured 2. Improved 4. No change 4.

Not many of the children's parents complained of cough, and when they did it was attributable to two main regions: nasopharyngeal and chest. Nasopharyngeal barking cough may be due, amongst other reasons, to discharge from infected adenoids, or to mouth-breathing causing a dry throat, and less often to large tonsils. It is readily improved by removing the offending structures and by nose-breathing instruction. The other type of cough—of pulmonary origin—may be due to infection passing down

from the throat into the lungs or to cold air from mouth-breathing. In this series there is one child whose father is convinced that removal of the tonsils and adenoids was a major factor in preventing repeated attacks of bronchitis. Years ago one often heard it said that infection was more likely to pass to the lungs if it were not caught up in the tonsils. Such a belief seems to have died a natural death, and perhaps this series will serve as one more nail in the coffin since in no case were more coughs or chest infections attributed to the absence of the tonsils and adenoids.

ALLERGIC MANIFESTATIONS

Number of children 7. No change 6. Improved 1.

An allergic child's tonsils and adenoids should be removed only on their own demerits as sometimes infection in them may precipitate an allergic attack.

GENERAL HEALTH

Number of children 50. Improved 35.

The removal of tonsils and adenoids, if it improves or cures some of the illnesses which indicated the need for the operation, must have, to that extent, a good effect upon the general health of the child. Apart from that it has often been observed that there is an improvement in growth and well-being, which is sometimes most impressive. It seems that doctors as a whole are rather critical of the health and growth of their own children, but it is gratifying to find the parents of 35 out of these 50 children asserting that they have benefited generally, some very greatly.

SATISFACTION WITH THE OPERATION

Number of children 50. Satisfaction 40. Partial satisfaction 6.

No satisfaction 3. Adverse criticism 1.

The question of being satisfied or not with the result of the operation was not put directly to the doctor-parents but they were asked for a general comment and from this it transpires that the parents of 40 were satisfied, those of six did not express themselves as feeling that the operation had achieved all they had hoped and three thought there was no benefit. One, a psychologist who described his child as an 'individualist', hopes that he may prevent permanent harm resulting from the child's separation from her parents; he was unfortunate not only because his child, of ten years, was very unhappy in hospital, but also in her being one of the three out of 35 children with otitis media who were not improved as a result of the operation.

GENERAL CONCLUSIONS

The removal of tonsils and adenoids is now under one of the clouds of disfavour which have obscured its merits for a few years at a time on several occasions during the present century. This seems particularly unwarranted at the present time when it is carried out with much more care and safety than in the past. If the operation is improperly performed and pieces of

tonsil and adenoid are left behind the patient is usually worse off than if nothing had been done, but such sad occurrences, although they happen, are much less frequent than they were. More painstaking care is still called for, particularly in the removal of adenoids (the most difficult part of the operation) because injury to the delicate muscles of the upper pharynx may lead to irreparable damage of the first sphincter of the respiratory-alimentary tract, and incomplete removal to worsening of the ear condition which possibly dictated the need for operation. Tonsil remnants are often more badly infected than the untouched tonsil, and cause more trouble.

The acute illnesses due to infection of the tonsils and adenoids—tonsillitis, peritonsillar abscess, otitis media and mastoiditis possibly leading to lateral sinus thrombosis and meningitis—can mostly be evaded by the prompt use of the chemotherapeutic drugs or antibiotics. This is a great advance which we all appreciate, and none more than those whose misfortune it was to deal with them. But it seems a little doubtful if all minor infections should be treated with these powerful drugs, and even more doubtful if it is wise to use them as maintenance drugs over long periods to 'maintain' freedom from infection. Do children now grow up without having had a good opportunity of developing natural immunity to common infections, so that they are often ailing rather than occasionally ill? No doubt tonsillitis was a sharp illness, if short; but children recovered from it before the modern drugs were discovered, and perhaps upper respiratory infections left the child with more immunity than he now gets a chance to acquire. It is always possible to resort to antibiotics and chemotherapy if an infection threatens to get out of hand, and by a conservative use of such agents it may well be that fewer strains of resistant organisms will be bred.

The tonsils and probably the adenoids are a small part of the defensive and immunizing mechanism of the body. They suffer heavily in the fight against invading organisms. The object should be to remove them only when they are judged to be doing more harm than good, when the illnesses dependent upon them outweigh the probable ability of the damaged organs to continue efficiently their proper role of defence. The results of the operation depend upon the proper selection of the cases and the proper execution of the operation. The children in this series were carefully considered by their parents and the surgeon, and the results seem to have justified the means.

The emphasis laid on infection and function must not cause us to ignore the mechanical troubles which may result from the large size of tonsils and adenoids which is the deciding factor against them in a minority of cases. Nor must the over-simplification of a short survey blind us to other causes of some of the symptoms which have been discussed. It was hardly possible, and perhaps unfairly misleading, to avoid reference to nasal sinusitis when discussing colds, nasal obstruction, nasal discharge and cough.

POLIOMYELITIS AND THE OPERATION

It would be inopportune to refrain from mentioning poliomyelitis when writing about the tonsil and adenoid operation. If a patient is infected with the poliomyelitis virus it tends to settle in those motor neurons which are in a poor state, whether due to fatigue or to a local injury in that particular part of the body which they serve. Hence great general fatigue is said to predispose to widespread paralysis, and local trauma may determine paralysis of the muscles in the injured region of the body. The nerves which supply the region of the tonsils and adenoids are the 9th and 10th cranial nerves, springing from the medulla oblongata, and so the trauma of the tonsil and adenoid operation may lead to that form of poliomyelitis which causes paralysis of the vital centres in the bulb. The same danger lies in any operation in the region of the naso- and oro-pharynx. Public attention, however, has been focused on the tonsil and adenoid operation because fatalities due to bulbar paralysis have occurred and been noted following it, but only because it is much the most frequent operation carried out in this region. It is obviously unwise to carry out any operation on the mouth or throat in a district where the incidence of poliomyelitis is high, because the chances that the patient has already been infected with poliomyelitis, or will become so before the wound is completely healed, are greater then. An immunizing injection against poliomyelitis should not be given within six weeks before or after a tonsil operation.

SUMMARY

Advantages are claimed for studying the results of the tonsil and adenoid operation upon a small series of doctors' children rather than upon a larger unselected series where observations would not be so accurate.

A high proportion of cures and improvement is shown for the well-recognized complaints which called for the operation: tonsillitis, sore throats, otitis media and deafness, cervical gland enlargement and severe colds. It was particularly gratifying to find so many children having fewer and less troublesome colds following the operation. There was an improvement in the general health of the majority of the children and the doctors of 40 of the 50 children were well satisfied with the result of the operation upon their own children; six were not so certain of great benefit, and four seemed to think it had not been worth while.

Modern opinion upon the indications for operation is considered, emphasis being laid on the much greater value of the history of illness than on the examination of the tonsils and adenoids.

There must be convincing evidence that they are doing more harm than good before their removal is advised.

The relationship between poliomyelitis and the tonsil and adenoid operation is explained.

ACUTE EPIGLOTTITIS SUPRAGLOTTITIS

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THERE is no more alarming experience for a conscientious general practitioner than to be confronted, after an urgent call, with a dead or dying child whom he has seen some hours previously and diagnosed as suffering from a simple infection. The best example of such an occurrence is the Waterhouse-

Friderichsen syndrome (meningococcal septicæmia). This is an uncommon but regular annual entry among the causes of unexpected sudden death discovered by those who carry out medico-legal necropsies for the Coroner. Most general practitioners can recollect in their practice an instance of a young child dying unexpectedly in these tragic circumstances. To this must now be added acute laryngeal obstruction from acute epiglottitis (supraglottitis) due to *Hæmophilus influenzae* (type B).

EARLY CASES

It was in 1950 that at necropsy one of us (F.E.C.) saw an appearance of the epiglottis which seemed to be so localized

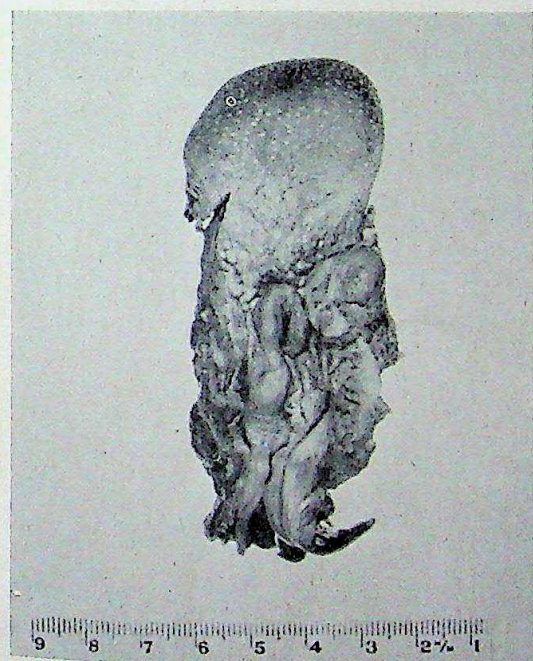


FIG. 1.—Example of brawny œdema of the epiglottis in a typical fatal case.

as to suggest some specific disease. This lesion consisted of a brawny œdema of the epiglottis (fig. 1) causing acute laryngeal obstruction. No other organic changes were noted on naked-eye or on histological examination, but the histological appearance of the epiglottis was one of an acute inflammatory reaction with a cellular infiltration which appeared at the time to be by round cells but were, in fact, immature polymorphonuclear cells. Surface bacteriology showed no organism which could be really incriminated. The history was one which has since proved to be typical of the disease:—

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A male child, aged 5 years, was perfectly healthy at 8 a.m. While having breakfast he complained of 'pain in the throat and back of the neck'. The family doctor was called and found a temperature of 103°F . (39.4°C .) but no physical signs. The pharynx appeared to be normal. During that day the doctor called again at least three times and although the child persistently refused solid food, he still could find no obvious physical signs. At 11.30 a.m. the child had a sudden convulsion and died.

In February 1950 the following two cases came under the care of one of us (H.M.J.) within a few days of one another.

A female child of 1 year 8 months was admitted to hospital with extreme stridor and died within a few minutes of admission. The previous day she had suffered from a slight cold and soreness in the throat. Two hours before admission she had suddenly had a choking fit and stridor and was rushed to hospital by her parents.

A female child, aged 2 years, was admitted with severe stridor which had been present for six hours before admission. She breathed with difficulty and there was expiratory stridor accompanied by severe intercostal recession. X-ray examination of the chest was clear. Laryngoscopy showed gross oedema and redness of the epiglottis and arytenoid cartilages. The white cell count was 16,000 per c.mm., with an excess of lymphocytes. An intratracheal tube was left *in situ*, antidiphtheritic serum was administered with penicillin, 100,000 units three-hourly, and chlor-tetracycline, 0.125 g. six-hourly. She collapsed and died 48 hours after admission. A culture swab taken direct from the larynx showed hæmolytic streptococci.

Both these cases were reported to the Coroner and a necropsy was carried out by one of us (F.E.C.). Both showed a very swollen epiglottis and supraglottic oedema above the vocal cords. There were no other obvious changes in any of the other organs.

In the light of this experience, the cases were discussed by us in some detail. It was determined that if a further case presented itself, in addition to medical treatment early tracheotomy would be far better than intubation and would mechanically by-pass the obstruction in the larynx. It was more than six months before such a case was admitted to the Ear, Nose and Throat department of the hospital. In the meantime further cases were seen in the course of routine post-mortem examinations and eventually *H. influenza* (type B) was isolated from culture of the epiglottis in two cases.

REVIEW OF LITERATURE

A search of the literature showed that before the 1918 pandemic of influenza, laryngeal diphtheria was thought to be the only cause of acute infectious 'croup' causing acute laryngeal obstruction. In the 1918 epidemic, however, it was recognized that there were other non-diphtheritic infections causing acute oedema of the larynx, glottis and subglottic regions. To this condition the term acute laryngo-tracheo-bronchitis was applied. More recently it was noted that among these cases were some in which the acute inflammation and oedema were localized to the supraglottic, arytenoid and epiglottic regions, resulting in acute laryngeal obstruction. A case of septicæmia with acute laryngitis due to *H. influenza* was described by de Nevasquez (1942), but apart from that the condition had not been recorded in England. On the other hand, in the United States reports had been published of epiglottitis due to *H. influenza* (type B). In 1941, Sinclair reported ten cases; in 1942, Alexander ten more; in 1943, Du Bois and Aldrich reported four; Stephen

reported one in 1946 and finally Davis three in 1947. The fullest description is that of Miller (1946) who analysed the admissions into the Los Angeles Children's Hospital during 1946, when there were eight cases.

Rabe (1948) revived the term acute infectious croup and analysed 347 cases admitted to hospital between 1937 and 1946. He divided them into three categories: (a) Diphtheritic. (b) *H. influenzae* (type B). (c) 'Virus' croup. Twenty-eight fell into the second category.

In December 1950, a further case was seen (H.M.J.):—

This was in a boy aged 5½ years. Sixteen hours before admission he complained of soreness in the throat, cough and hoarseness. This was followed two hours before admission by stridor and difficulty in breathing. An x-ray of the neck and chest was taken to exclude a possible foreign body: the films were clear. Laryngoscopy showed a brawny red swollen epiglottitis. A bronchoscope was passed, blood-stained mucus aspirated from the trachea, and tracheotomy was performed. Following on operation chlortetracycline was given by mouth; steam inhalations were used to moisten the air and after a stormy first two days he made a good and uneventful recovery. A swab taken from the larynx in this case grew *H. influenzae* (type B) sensitive to chlortetracycline and slightly sensitive to penicillin.

In 1953, Camps reported a series of 19 cases seen at necropsy between 1944 and 1952, from two of which *H. influenzae* had been isolated by deep culture. Comparisons of age and seasonal incidence suggested that they were the same condition as that described by the various American authors. Since then five more cases have been seen, from all of which *H. influenzae* (type B) has been recovered and in one case only a purulent meningitis due to the same organism was demonstrated—a more advanced stage of that described previously (Camps, 1953).

TWO CASE RECORDS

Interest in the subject of epiglottitis was reawakened when the following two cases, which were successfully treated, were encountered by H.M.J.

A male child, aged 2 years 1 month, was admitted to hospital on December 3, 1955. Eight hours before, on the morning of admission, the child had been off colour and would not eat. At 5 p.m. on the same day he suddenly developed great difficulty in breathing and this gradually got worse. By 11 p.m. the same evening, when first seen by the surgeon, the child had a grey pallor, extreme stridor, and recession of the lower ribs and supraclavicular areas. Breath sounds over the whole chest were absent. Laryngoscopy showed a red, swollen epiglottitis. Immediate tracheotomy under general anaesthesia was carried out. Chlortetracycline was given: 0.125 g. four times a day—intravenously on the first day, and then by mouth on the following and subsequent days. The child made an uninterrupted recovery and the tracheotomy tube was removed on the tenth day.

A female child, aged 3 years 5 months, was admitted *in extremis* on December 23, 1955. The history, as given by her own private doctor, was as follows: 'This little child was first seen by my deputy on the evening before her admission to hospital. He found her coughing a little and complaining of some shortness of breath. He was not worried about her condition and prescribed an antispasmodic cough mixture. I saw her next morning and she seemed quite comfortable, her throat was then a little injected and her chest revealed an odd rhonchus. There was slight pyrexia: 100° F. (37.8° C.). I was next called to see her at about 8 p.m. on the night of her admission and was greeted on arrival with a child desperately ill: she was cyanosed and gasping for breath but with scarcely any air entry sounds to be heard. Her throat looked rather red and swollen. In view of the extreme urgency of the case, I took the child along to hospital myself in my car'.

Examination at the hospital showed a child almost moribund, with great difficulty in breathing. Laryngoscopy showed an œdematous red epiglottis. Immediate, unsterile, urgent tracheotomy was carried out, with improvement in the child's condition. Chlortetracycline, 0.125 g., was given four times daily: intravenously on the first day and then by mouth. The child made a good recovery and the tracheotomy tube was removed on the tenth day.

It is as a result of these successes that it is felt that the attention of general practitioners and pædiatricians should be drawn to the existence of the condition, how to diagnose it and the treatment to be instituted in order to save the patient's life.

ETIOLOGY AND PATHOLOGY

Acute epiglottitis may be defined as 'An acute inflammatory œdema of the epiglottis causing laryngeal obstruction due to swelling and immobilization of the structure'.

In our series of 29 cases there was a slight predominance of males (17 males and 12 females). More than half the children (15) were between the ages of two and five years. Four were under one year of age, five were aged 1 to 2 years, four were aged 5 to 6 years, and only one (aged 12 years) was over the age of 6 years. There was a marked preponderance of cases (25) in the winter (October to March).

The specific infecting organism is *Hæmophilus influenzae* (type B). In most of the cases, the lesion has been limited to the epiglottis. Histologically there is a diffuse infiltration with immature polymorphs with some inflammatory œdema. On account of the anatomical structure of the epiglottis, that part of the structure which has the mucosa closely applied to the cartilage shows less swelling. On occasion the organism has been demonstrated in sections and all recent cases (i.e. since 1951) have yielded pure cultures of *H. influenzae* (type B) on deep culture (introduction of saline into the submucosal tissue after searing). There appears to be no extension upwards into the lingual lymphoid tissue or to the pharynx, nor is there any extension down into the subglottic region: in other words, it is a pure supraglottic lesion. Severe ulceration of the mucosa has not been seen, but careful examination has shown slight surface ulceration in one or two cases. In none of the cases has any remote lesion been demonstrated other than meningitis (two cases); in both of these the initial diagnosis was *Hæmophilus influenzae* meningitis and purulent fluid had been withdrawn on lumbar puncture.

In the first case the naked-eye appearance of the epiglottis appeared to be within normal limits but sections showed round-celled infiltration whilst in the second case the child died suddenly with laryngeal obstruction and the epiglottic lesion (naked eye) was typical.

Toxic changes have not been obvious but in spite of this, after initial relief of the obstruction, immediate recovery has not taken place although there is much improvement. The child has remained ill for anything up to forty-eight hours. It is clear that there has been a septicæmia; the American workers have obtained positive blood cultures.

CLINICAL PICTURE

The history, several typical examples of which have already been quoted, is characteristic. The early symptoms are insignificant, slight soreness in the throat, poor appetite and slight cough being the only complaints. Clinical examination of the chest reveals no significant changes. Pyrexia is often high. These are followed a few hours later by the sudden onset of acute upper respiratory obstruction and stridor, accompanied by shock and severe prostration, and a rapidly progressive course of the disease. The reason for the apparent suddenness in the onset of these dangerous symptoms is that the laryngo-pharynx is a relatively large space into which the swollen tissues can expand and it can accommodate extreme swelling of the structures without much difficulty. Because of this, the doctor is led to believe that he is dealing with a mild case of 'croup'. Here lies the danger, for with lightning-like suddenness the patient's condition can be gravely altered. A slight increase in the already extreme oedema, a fit of coughing, or movement may displace the swollen and loose supraglottic structures. They may be drawn into the glottis, between the vocal cords and quickly plug the lumen. There is a sudden sense of choking and the patient responds with frantic inspiratory efforts which make matters worse and jam the swollen tissues down ever more tightly. The patient is often asphyxiated before help can be given.

In those cases reaching hospital, there is stridor, both inspiratory and expiratory, with intercostal retraction and retraction of the supraclavicular areas. Examination of the chest reveals absence of breath sounds.

The sudden onset of these severe symptoms, accompanied by a complaint that the throat hurts on swallowing, is typical and it has often been suspected that the child has inhaled a foreign body, a sweet or a bone. When time was available, this possibility was excluded by an x-ray of the chest and soft tissues of the neck.

DIAGNOSIS

This depends in the first place upon recognizing that the condition exists and suspecting it in all young children suddenly taken ill. The rather sudden onset of upper respiratory obstruction, usually with high fever and slight or absent premonitory symptoms, is characteristic. Symptoms of shock or prostration are out of proportion to the short duration of the respiratory difficulty.

The appearance of the epiglottis confirms the diagnosis. Firm pressure with a spatula at the base of the tongue will sometimes reveal the swollen epiglottis. This was found to be difficult and in the cases quoted which came to operation a laryngoscope was gently inserted and found to be necessary to get a good view of the epiglottis and larynx. Nastruck (personal communication), however, does not approve of the use of the laryngoscope as he has seen sudden collapse after its use but states that the epiglottis can be seen by drawing the tongue forward. No harm, however, appears to have been done in our cases by laryngoscopy.

THE TREATMENT OF HÆMORRHOIDS

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'And telling me the sovereign'st thing on earth was parmaceti for an inward bruise'.
—*Henry IV, Part I*

THIS titbit of medical news voiced by a 'popinjay' at the end of a hard-fought battle infuriated the exhausted Harry Hotspur much in the same way as today the same remark might move a medical practitioner to derisive comment. It is not clear from the context whether the 'inward bruise' referred to was a bruise earned in the battle since it was an irrelevant remark. Might it not have had some other meaning? If a pile be an inward bruise, then there is historical precedent going back three hundred-and-sixty years for the treatment described here.

Parmaceti, the modern name for which is spermaceti, is a wax derived from the head of the sperm whale. Its main ingredient is cetyl palmitate or cetaceum. This is the active principle in 'parmacetyl' tablets, which also include small amounts of ethyl hydroxyethyl cellulose and magnesium hydroxide, to combat the constipation so often associated with piles.

At first sight, the oral route seems an unnecessarily long approach to a pile, but it has obvious æsthetic and hygienic advantages, and it avoids the pain of inserting a suppository against an inflamed pile. The active principle in oral treatment must not be absorbed to any great extent in its passage through the bowel if it is to reach the rectum in adequate concentration to be effective. McIsaac (personal communication) has studied the behaviour of waxes in the bowel and reports that not more than 25 per cent. of cetaceum is absorbed in transit and that at least 70 per cent. arrives in the rectum unchanged.

SCOPE OF INVESTIGATION

To exclude the possibility that any beneficial effects of treatment were due to the small amounts of aperients in the tablets, cachets containing equivalent weights of pure cetaceum were made up and their effects compared with those of the tablets. Batches of ten consecutive patients were given either tablets or cachets. Twenty-five patients received tablets and twenty-five had cachets.

Treatment consisted of taking tablets or cachets morning and evening: three for the first two doses and thereafter two at a time until a total of ten or twelve had been taken. If a first course was not effective within a week, a second similar course was given. Alcohol and aperients were forbidden. The tablets were too large to swallow whole with comfort and were therefore crushed in a spoon and then swallowed with a full glass of water.

Abdominal, rectal and proctoscopic examination was carried out at the
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first visit and again after one week and at any subsequent visit, unless pain or anal spasm made it impracticable. In such cases proctoscopy was postponed until a later visit, when it could be performed without distress. Symptoms complained of included pain, pain on defæcation, irritation, bleeding, discharge and prolapse. Cases were classified according to the state of prolapse: 1st degree where there was no prolapse; 2nd degree where prolapse occurred only after defæcation and spontaneously reduced; 3rd degree where the piles remained prolapsed.

RESULTS

The results are summarized in table I. Subjective relief was a marked feature but a successful result was not claimed unless it could be seen that there was also objective improvement. Bleeding had to stop and the inflammation to subside. It was not required that prolapse should be improved.

	Successes		Failures		No. of cases	
	'Parmacetyl'	Cetaceum	'Parmacetyl'	Cetaceum	'Parmacetyl'	Cetaceum
1st degree	12	11	3	1	15	12
2nd degree	4	2	1	0	5	2
3rd degree	3	5	2	6	5	11
Total	19	18	6	7	25	25

TABLE I.—Comparison of results obtained with 'parmacetyl' tablets and cachets of cetaceum in treatment of hæmorrhoids.

The results obtained with the tablets and the cachets were equally effective. No side-effects were experienced by any of the patients.

1st degree piles.—Fourteen of the 23 successfully treated patients in this group responded by the end of the first course. The other nine required two courses. They included two with granular proctitis and one with inflammation and ulceration of the sigmoid colon. This patient was given propantheline as well as 'parmacetyl' and both colon and piles cleared up in a fortnight. Three cases showed a delayed response; that is, they resolved after a period of about two weeks after the end of treatment. There were four failures, all due to the persistence of constipation.

2nd degree piles.—Four of these seven patients were relieved at the end of one course. One relapsed a month later, but responded to another course in a week. Another patient had a granular proctitis which required two courses before it subsided.

3rd degree piles.—In this group symptomatic relief was more marked than objective improvement. Bleeding stopped easily enough but the prolapsed piles tended to remain inflamed. Nevertheless, in eight out of the 16 patients, the condition completely subsided and in three the piles were reduced to 2nd degree prolapse. One patient relapsed after three weeks and again after three months, responding each time to further courses of treatment. One relapsed after four months, but responded to another course.

DISCUSSION

Before treating a patient with piles it is important to establish the cause, particularly excluding carcinoma of the rectum. Careful history-taking with particular reference to change in bowel habit, weight loss and dyspepsia is important. Physical examination or instrumentation should reveal any mass in the rectum. Proctoscopy is important in order to assess the state of the piles which are not palpable unless thrombosed.

Medical treatment cannot cure a prolapsed pile. All third-degree and most second-degree piles require surgery. Some first-degree piles have reached such a condition that surgery offers the best hope of a permanent cure. Constipation must be corrected or medical treatment is doomed to failure. The aim, then, of medical treatment is to give subjective relief, to stop bleeding and to cause inflammation to subside. Within these limits cetaceum proved a successful form of therapy. There was little to choose between the tablets and the cachets, but the tablets were easy to take and had the added advantage of containing a small dose of aperient.

'Parmacetyl' tablets are effective in most cases of 'acute piles'. Nearly all first-degree piles will respond to them. Bleeding in second- and third-degree piles is soon controlled. Inflammation in these degrees is more difficult to bring under control but there is quite remarkable subjective relief. They are valuable in the preoperative treatment of piles in that there is considerable reduction in the inflammation, if not complete resolution. The presence of granular proctitis does not make the prognosis worse as it responds readily to this form of treatment. The response is in fact so good that it suggests that 'parmacetyl' by mouth might be effective in conditions in the colon such as ulcerative colitis but this has not yet been investigated.

SUMMARY

A new form of treatment for piles, oral 'parmacetyl' tablets, was investigated. A similar number of cases was treated with oral cachets of cetaceum, the wax used in 'parmacetyl'. Fifty cases were treated in all.

Both forms of treatment were equally successful, confirming that it was the wax which was effective: 23 out of 27 cases of 1st-degree piles settled down; six 2nd-degree and eight out of 16 3rd-degree cases responded satisfactorily.

It is not suggested that this treatment can replace surgical therapy, but it is a valuable preoperative measure.

Its best use is for attacks of 'acute piles' and for 'bleeding piles', but the remarkable subjective improvement noticed after its use makes it valuable even in chronic cases.

No side-effects were experienced.

I wish to thank the many general practitioners of North Kensington and Hammersmith who helped by sending me cases; Mr. L. A. Ives, surgeon at this hospital, for his observations on the cases upon which he operated; and Dr. R. Mackarness and the E.G.H. Laboratories who provided the tablets and cachets.

CONFUSING THE ISSUE

PSYCHOSES AS SYMPTOMS OF CANCER

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AMID the flood of 'senile and demented' elderly patients, who today occupy about a quarter of the total hospital beds in the country, there is a definite percentage whose mental symptoms cloak bodily disease and confuse the issue until a post-mortem examination establishes the diagnosis. A recent series of necropsies has shown a group of patients with cancer whose obvious mental symptoms had only made confusion worse confounded. Their histories illustrate some of the peculiar problems which distinguish geriatrics from the ordinary run of general medicine.

CASE RECORDS

M.J.B. was admitted to St. John's Hospital, Battersea, as an alleged senile dement. She was filthy, neglected, wasted and pale. Extensor plantar responses and absent tendon reflexes raised the possibility of pernicious anæmia with subacute combined degeneration of the spinal cord. Death took place on the third day after admission and necropsy was performed. This revealed an ulcerating carcinoma of the stomach with secondaries in liver, spleen and lung. Some cerebral softening was also present.

E.E.F. came into hospital on account of mental confusion. She became comatose and died without presenting any definite physical signs. At post-mortem examination we found a carcinoma of the rectum, with secondaries in the liver. The brain appeared normal.

S.M.F. presented headache, restlessness and delusions. His necropsy diagnosis proved to be carcinoma of the prostate, with secondaries in liver and aortic glands.

F.M., admitted as 'senile, confused, incontinent', was found to have a carcinoma of the ovary, invading the other abdominal organs.

M.B., labelled 'senile dementia', showed delusions and would not let anyone look after her. Apart from some bronchitis, the only physical sign was a small nodule in one breast. At necropsy this proved to be malignant, with secondary deposits in pleura and lungs. The brain showed some wasting and atheroma of vessels.

M.A.E. was also admitted as 'senile dementia'. She died two days later. A large malignant ulcer of the stomach was found at necropsy, in addition to diverticulitis with peritonitis and marked calcification of aorta, mitral and aortic valves.

DISCUSSION

All these patients were aged between 80 and 90 years. In every one of them the mental symptoms completely overshadowed the physical signs. Most of them were non-cooperative and difficult to examine. None of them was suitable for careful pathological investigation or x-rays. In many instances the symptoms were of recent origin, so that the cases appeared to be senile psychoses. It is therefore important to realize that in old age a new growth can have mental confusion as its chief presenting symptom.

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GENERAL PRACTITIONERS' FORUM

THE HOME NURSING SERVICE

A PLEA FOR 'DISTRICT ASSISTANT NURSES'

By R. L. KITCHING, M.B., B.S.

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THE general public are beginning to realize how much suffering there is that could be relieved by a better home nursing service, but there is little evidence that the authorities have any idea of the extent and urgency of the problem or how to solve it. This is borne out by the Report of the geriatrics joint subcommittee of the British Medical Association (1955). There are 92 paragraphs and 21 recommendations and the home nursing service is disposed of in one paragraph of 12 lines (compared with 24 lines required by chiropody). The shortage of nurses is dealt with very quickly and easily:

'... establishments should be reviewed in the light of the needs of the elderly sick and infirm. It is recommended that a greater number of male nurses should be recruited to these services. In addition, a proportion of both male and female State-enrolled Assistant Nurses should be employed for duties within their scope. ...'

INSUFFICIENT DISTRICT NURSES

The shortage of district nurses is an extremely serious matter and it is getting worse; it will certainly be many long years before there are enough district nurses so the sooner the question of assistants is re-examined the better. The solution of the problem lies in two facts: much of the district nurses' work could be done by less well-trained assistants, and there is a good deal of nursing that the district nurses cannot do which the assistants could do very well and which would be of the greatest comfort to the patients. For example, a district nurse cannot sleep in a patient's house and she cannot take duty as a night-nurse, but an assistant could sit up at night and would be a great comfort to the patient and a great help to the relatives and the doctor. There is much she could do with very little training; there are all sorts of small services and kindnesses for which patients are often inexpressibly grateful and which are true nursing. There are so many new therapies these days that the curative value of kindness is apt to be overlooked in the training schools. Another example of work which a district nurse cannot undertake is to be at a patient's house at a given time each day, although this sometimes makes a great difference to the patient's welfare, as in the case of old people who are getting helpless and soon become bed-fast if they are not washed and dressed punctually each day.

There is one service that an assistant nurse could render which is exceptionally important because it is one which the district nurse has to refuse.

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Owing to the shortage of nurses all the district nurses are now midwives and are therefore not allowed to prepare the dead for burial. This is a serious matter because in these days there are no other trained women to do it and relatives are often extremely distressed about it. Trained assistant nurses would be able to render a valuable service in this way.

NURSES AND FAMILY PRACTICE

The prevention of suffering is not the only reason for getting assistants for the district nurses as soon as possible. A second reason is that it is important to get back to the old-fashioned family practice before it is completely destroyed. The whole Welfare State depends ultimately upon the quality of the family doctors and it is not realized by the authorities that it is quite impossible to get good family doctors without good family practice. For that there are three main requirements and we have only got two of them. We have the houses we want, with every conceivable facility for treating patients at home; and we can get a consultant out whenever we want one. The third essential is a nurse and in the old days we could always get one. She was usually an untrained amateur but she was often a very good nurse, and she made it possible to treat the patient at home. But nowadays there are so few nurses that nearly all our interesting cases have to be sent to hospital and therefore we cannot get any good family practice. And, of course, if more patients could be treated at home there would be other great benefits: it would set free hospital beds that are urgently needed; and it would be the greatest comfort to patients who dread being sent away, especially to those who ask for nothing but to be allowed to die at home—the last freedom. And surely a natural, inalienable right.

The first step towards a solution of the problem is to appreciate how big it is and how dreadful it is. The present neglect of the aged sick is as disgraceful as the callous disregard for the safety of children on the roads. Miss E. A. B. Davis reported on her examination of the home nursing problem in February 1955. She envisaged a service of state-trained nurses helped by voluntary workers, bath attendants, night attendants, sitters-in and so forth. A mixed team of this sort is probably the best that can be done to meet the acute emergency, but it would never do as a permanent home nursing service.

IMPORTANCE OF QUALIFIED NURSES

In a permanent service there must be a rigid rule that if a district nurse wants help in *nursing* the patient the helper must be a nurse; if she wants help in the house she can get a Home Help who is an extremely valuable member of the Public Health Department but is not a nurse. There must be the same distinction between nurses and other helpers as there is between doctors and other helpers. A nurse is a woman who has certain qualities and is trained; the training is a matter of discipline, knowledge and skill; the skill is acquired by constantly practising the techniques she was taught

in hospital. Nurses must be qualified and registered by a controlling authority. It is extremely important that the local government authorities should take every care to avoid any action that might seem to countenance unqualified nurses. The Civil Defence authorities seem to need watching on this point. Nurses must be qualified but that is not to say that there can be only one qualification.

The fact that there is a shortage of full-time nurses does not mean that there must necessarily be a shortage of part-time nurses. There are at present many women who want to earn a pound or two a week by part-time work and a few preliminary inquiries indicate that enough of them could be recruited to help in the home nursing service if they were appealed to in the right way and if the working conditions were made attractive. Of course, if there were enough State-enrolled assistant nurses (S.E.A.N.) they would solve the problem at once but there are none to be had and it takes about two years to train them.

DISTRICT ASSISTANT NURSES

It would be for the General Nursing Council to decide whether it would be better to shorten the training of the S.E.A.N. or to establish a new service of part-time 'district assistant nurses' with a much shorter training. Forty years ago it took four years to train a nurse and seven years to train a soldier, but it was found in both world wars that efficient soldiers could be trained in about nine months. No doubt nurses could be trained as quickly in war time but it would be difficult to get the necessary discipline in peace time. Discipline could not be enforced without some system of punishments and that seems hardly practicable at present, quite apart from other considerations. Self-discipline can be learnt reasonably quickly if it seems worth while, but on a national scale in peace time it would require a long process of education. It seems certain therefore that the shortage of nurses will not be made good in our time unless it is treated as a national emergency—unless, in fact, women are conscripted.

It will be said, of course, that one volunteer is worth three conscripts. The reply to this is twofold. In the first place, experience in two world wars proved that it is not true; and secondly, we cannot go on any longer waiting for volunteers while old people are suffering as they have not suffered for a hundred years.

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CURRENT THERAPEUTICS

* CX.—THE USE OF BEMEGRIDE IN BARBITURATE COMA

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THE discovery that nalorphine (*N*-allylnormorphine) has a specific and selective antagonism to the respiratory depressant actions of morphine has provided an effective means of reversing the most dangerous effects of acute poisoning with morphine and similarly acting substances, such as methadone. The mode of action of nalorphine in reversing morphine-produced respiratory depression must remain a matter of conjecture until more is known of the action of morphine on the central nervous system, but the chemical structure of nalorphine and morphine is so similar that it must be considered possible that the receptors in the central nervous system which are affected by morphine can be blocked by nalorphine. This pharmacological relationship between the two drugs would be similar to that which exists between acetylcholine and atropine. It is not surprising that nalorphine is ineffective in counteracting the respiratory depressant effects of barbiturates since the action of barbiturates on the central nervous system is different from that of morphine.

Whilst acute morphine poisoning is now rather rare, the frequency of barbiturate poisoning is a problem of growing importance, and attention has been drawn to the increasing number of deaths from this cause (*Lancet*, 1951). As this death rate only reflects the much larger incidence of acute barbiturate poisoning which does not end fatally, and which has resulted from the extensive prescription of this group of sedatives and hypnotics, the therapy of barbiturate poisoning is now a problem of much greater magnitude than that of morphine poisoning.

Before discussing bemegride, the recently introduced analeptic, the treatment of barbiturate poisoning in general will be discussed.

THE TREATMENT OF BARBITURATE POISONING

The treatment of barbiturate-induced coma is a matter which has aroused some controversy, and in the past the issue has been clouded by the fact that danger to life in any case depends, broadly speaking, not only upon the amount of barbiturate consumed and absorbed, but to a large extent upon the nature of the barbiturate. The outlook in poisoning from a drug of short or medium duration of action is invariably better than that from poisoning by a long-acting member of the group. The features of barbiturate coma which combine to lead to a fatal outcome are: (1) Anoxæmia primarily due to respiratory depression but aggravated by obstruction of

the respiratory passages by mucus and collapsed soft tissues which results from the loss of laryngeal and pharyngeal reflexes. (2) Hypotension produced by central depression and possibly by certain effects on the peripheral autonomic nervous system. (3) Infection of areas of pulmonary atelectasis leading to fatal broncho-pneumonia. If this cycle of events can be broken by proper management so that anoxæmia and hypotension are prevented and renal function maintained, there is no theoretical or practical reason why even the most severe barbiturate coma should not recover, as in time the drug will be detoxicated or excreted, and recovery from coma will coincide with a decline in the amount of barbiturate in the blood (Wright, 1955).

It has become clear that analeptic drugs play a role of secondary importance in the treatment of barbiturate poisoning as compared with that of general measures designed to relieve or prevent anoxæmia. Treatment should be started as early as possible and requires skilled and constant supervision. This means that admission to hospital is necessary.

At the outset of treatment *gastric lavage* may remove a significant amount of unabsorbed barbiturate and should be performed in every case. A large-bore stomach tube should be used and, to avoid undue risk of aspiration of fluid into the lungs, lavage should be carried out with small volumes of fluid by means of an apparatus such as Senoran's evacuator. An adequate airway must be achieved by the aspiration of mucus and fluid from the tracheo-bronchial tree and soft-tissue obstruction be prevented by passage of an endotracheal tube if necessary.

Oxygen should be administered by a mask, nasal catheter or other method dictated by the state of the patient. The position of the patient is of importance and he should be nursed in a lateral decubitus position. The head-down posture is best avoided. In severe cases, in which tidal exchange is much reduced, respirations slow and cyanosis marked, complete apnoea may occur and respiration may have to be maintained by the use of an effective mechanical respirator. It is in the prevention of this complication that the new drug, bemegride, finds its greatest use.

When hypotension is marked, the blood pressure may be raised by the administration of plasma or a suitable plasma substitute. *Adequate fluid intake* should be ensured by the intravenous infusion of 2 litres of 5 per cent. glucose over twenty-four hours. Excessive intravenous fluid administration may lead to pulmonary œdema and cannot be justified on the grounds that it will accelerate the excretion of barbiturate, as the long-acting barbiturates are but slowly excreted by the kidney and the rate of excretion is not significantly increased by increasing urinary output. Throughout treatment the urinary output must be carefully observed and this is most effectively achieved by regular catheterization. The amount of urine secreted must be taken into account in determining the volume of fluid administered parenterally.

The risk of pulmonary infection is reduced by the prophylactic adminis-

tration of an antibiotic such as *penicillin*, and care should be taken to avoid damage to the eyes during the handling of the unconscious patient.

• There is general agreement on the value of the type of treatment outlined above but considerably less accord regarding the use of analeptics such as nikethamide, picrotoxin and amphetamine. Whilst these drugs have many protagonists, there is little convincing evidence of their effectiveness (Report to Council on Pharmacy and Chemistry, 1936, 1939; Eckenhoff and Dam, 1956).

The main danger associated with the use of analeptics is the risk of inducing convulsions with subsequent severe medullary depression. Cardiac arrhythmia may be induced and vomiting may occur with aspiration of vomited material. In anoxia surprisingly small doses of analeptics such as nikethamide may occasionally induce convulsions. The advantage to be expected from the use of analeptics is an increase in tidal volume and elevation of blood pressure. That these effects can be elicited is undoubted but they are short lived, and frequent injections must be given. In the case of picrotoxin, a considerable latent period elapses between the time of injection and the onset of its stimulant effect so that the result is somewhat unpredictable, and dangerous convulsions may be produced.

THE CHEMISTRY OF BEMEGRIDE

Bemegride ('megimide') was first synthesized in 1911 and was investigated by Shaw *et al.* (1954) as a barbiturate antagonist. It was found by animal experiment and clinical trial to be an effective analeptic in barbiturate poisoning, showing a much longer duration of action than analeptics hitherto employed. Bemegride is a white crystalline substance sparingly soluble in water with the following structural formula (fig. 1):—

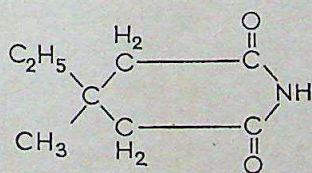


FIG. 1.

—Structural formula of bemegride.

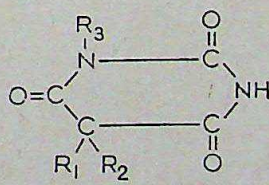


FIG. 2.

—Basic structure of the barbiturates. R_1 , R_2 , R_3 are radicals varying in different barbiturates.

This structure bears certain obvious similarities to the basic structure of the barbiturates (fig. 2).

THE PHARMACOLOGY OF BEMEGRIDE

In animal experiments it is found that bemegride antagonizes the hypnotic and respiratory depressant action of barbiturates in rabbits, dogs, rats and mice, with rather less dramatic effects in the cat. Given to an animal which has previously received an anæsthetic dose of a short-acting barbiturate,

bemegride causes an increase in respiratory rate and tidal volume associated with a return of reflexes and an arousal to consciousness; subsequently the animal may sleep but can be aroused by handling. Given to an animal not

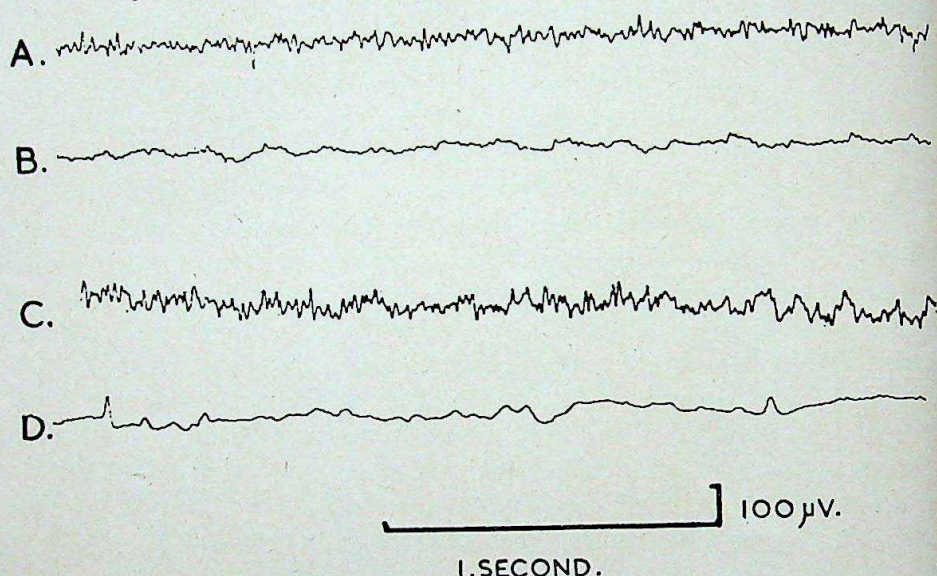


FIG. 3.—Electroencephalograms showing the effect of bemegride in a rabbit anesthetized with pentobarbitone. (A) Awake. (B) Pentobarbitone, 40 mg./kg. (C) 5 minutes after B. Bemegride 20 mg./kg. (D) Control. 5 minutes after B. No bemegride given (Cass, 1956).

under the influence of a barbiturate, a relatively small dose of bemegride will cause convulsions which can be stopped immediately by an intravenous administration of a barbiturate. If an animal is rendered comatose by the use of a long-acting barbiturate, bemegride will cause a significant increase in the rate and depth of respiration with restoration of reflexes and spontaneous movement. The duration of intensity of this effect depends upon the dose. Large doses of bemegride may induce such a high degree of hyper-excitability that in response to handling the animal may be thrown into convulsions. These effects in animals are similar to the effects in man.

It has also been shown (Cass, 1956) that bemegride restores the normal electroencephalographic pattern in rabbits when the electroencephalogram has been depressed by a barbiturate (fig. 3). On the other hand, the pattern of deep depression produced by other non-barbiturate sedatives and hypnotics is not affected by bemegride. A similar reversal of the electroencephalographic pattern of barbiturate depression in man by bemegride has been demonstrated by Louw and Sonne (1956). These observations suggest that bemegride may have a specific action in antagonizing the depressant effects of barbiturates on the central nervous system rather than a non-specific central stimulant action. Final conclusions on this latter question must, of course, await much fuller pharmacological investigation, both of the action of barbiturates on the central nervous system and of

bemegride, but the striking effects seen in animal experiments suggested the use of the drug in barbiturate coma in man. A striking and interesting feature of the action of this drug is that, by comparison with other analeptics such as nikethamide, the duration of stimulation of respiratory centre is much longer and the degree of response more easily controlled by varying the dose.

CLINICAL USE OF BEMEGRIDE

In 1955, Shulman *et al.* (1955) reported the effects of bemegride in barbiturate poisoning in man and recommended that, in addition to the usual general method of dealing with the comatose patient, treatment with bemegride should be supplemented by the use of amiphenazole ('daptazole') (2:4:diamino-5-phenylthiazole). The routine treatment recommended by these authors consists of slow intravenous infusion of 5 per cent. glucose, so that 10 ml. of 0.5 per cent. solution of bemegride (50 mg.) can be injected into the tubing leading to the intravenous cannula. This injection is repeated according to the needs of the patient every three to five minutes, each injection being preceded by 1 ml. of a 1.5 per cent. solution of amiphenazole. Amiphenazole is an analeptic which causes arousal in morphine narcosis and also shows to some extent an analeptic action in barbiturate coma, but subsequent experience with this form of treatment favours the conclusion that of the two drugs bemegride is by far the more active, and it is doubtful if amiphenazole contributes significantly to the efficiency of treatment. Clemmensen (1956) suggests that the bemegride should be given by continuous intravenous drip of 100 ml. of saline containing 500 mg. of bemegride over a period of thirty minutes, the injection being interrupted after 300 mg. have been given.

Following an injection of 50 mg. of bemegride in barbiturate coma in man, there is evidence of central stimulation. There is a marked increase in the rate and depth of respiration, an increase in the pulse rate and a rise in blood pressure, the colour of the skin and mucous membranes improves, and there may be evidence of arousal in that the patient responds to painful stimuli and deep superficial reflexes return. Swallowing and coughing may occur and tone returns to flaccid muscles.

The striking difference between the action of bemegride and analeptics such as nikethamide is seen in the duration of action of the former. The action of nikethamide is momentary, lasting two to three minutes, whereas the duration of action of bemegride is much more prolonged and the effect of a single injection may last for fifteen to twenty minutes or longer. The effect of a single 50-mg. dose of bemegride depends, however, upon the depth of central depression which in part at least depends upon the amount of the barbiturate in the blood, and it is necessary to repeat the injection of bemegride at intervals dictated by the response of the patient, the objective being to maintain the patient in a state of light coma. As might be expected, the dose required for this is smallest and the response most

dramatic in patients poisoned with a short-acting barbiturate. In many of these cases a central nervous system stimulant is scarcely necessary but, at the other end of the scale, in patients who have been poisoned by a long-acting barbiturate, and have been profoundly comatose for some time, frequent injections must be given, and if anoxæmia and hypotension have been severe and prolonged before the beginning of treatment, neither bemegride nor any other drug may be of any avail.

Because of the wide variation in the severity of barbiturate poisoning and of the influence on prognosis of factors such as the type and quantity of barbiturate ingested, the degree of absorption of the ingested drug, the time which has elapsed between the onset of the coma and the institution of treatment, the possible existence of previous addiction, and the fact, often unknown to the physician, that other central nervous system depressants have been taken, it is difficult to plan a suitably standardized clinical experiment to discover the value of a given form of treatment in barbiturate coma. A recommended treatment therefore tends to be favoured or neglected on the basis of impressions gained from relatively limited experience. There is, however, an increasing literature of published and well-documented evidence tending to show that in severe barbiturate coma bemegride is of undoubted value as a respiratory stimulant to counteract profound respiratory depression (Kjaer-Larsen, 1956) and that the beneficial effects are of much longer duration than those of nikethamide and other analeptics. At the same time, it is becoming apparent that significant as these effects are bemegride has little effect on the duration of unconsciousness; this is determined by the amount of barbiturate in the blood and is not influenced by bemegride, as there is no chemical interaction between the two drugs, nor does bemegride affect the rate of elimination of barbiturate.

SIDE-EFFECTS OF BEMEGRIDE

Convulsions.—In common with other analeptics bemegride may cause convulsions if given in excessive quantity. The convulsive state can be terminated by raising the blood barbiturate level by the injection of a small quantity of a short-acting barbiturate. This complication is seen more often in poisoning with short-acting barbiturates than in that which follows long-acting drugs. Shaw *et al.* (1954) recommend that during treatment with bemegride thiopentone should be readily available to meet this emergency. By proper care in the administration of bemegride, however, and careful observation of the response of the drug, convulsions during treatment should not occur. It is well recognized that generalized epileptiform convulsions may occur in barbiturate addicts when the barbiturate is rapidly withdrawn. This suggests the possibility that bemegride may cause convulsions by displacing barbiturate from specifically sensitive receptors in the central nervous system, an unlikely explanation, since addicts and non-addicts appear to be equally liable to this complication. Further, it has already been noted that other short-acting analeptics in excessive dose may

cause convulsions in barbiturate coma.

Vomiting.—If the dose of bemegride used is excessive, reflex activity may be enhanced to a degree sufficient to induce vomiting. This event in the unconscious patient is undesirable, as it may lead to the aspiration of gastric contents with consequent pulmonary complications. Vomiting during bemegride administration can be readily avoided by careful observation so that respiration is maintained without excessive reflex activity.

Psychosis.—Kjaer-Larsen (1956) has reported the occurrence of a delayed delirious psychosis in 15 patients out of a series of 50 cases of barbiturate coma treated with bemegride. The psychosis developed between the 1st and 4th day after recovery from coma, and mental disturbance was of a fairly uniform pattern characterized by visual hallucinations of colours and shapes, auditory hallucinations which often relate exactly to events in the patient's past, loss of orientation in time and space, and delusions which have a definite relation to previous experience. This psychotic state leads to considerable confusion and inattention and may last for as long as seven days. It is not exclusively seen in barbiturate addicts and is more likely to occur when large doses of bemegride have been used.

CONCLUSIONS

In the treatment of barbiturate coma general management directed to the relief of anoxia, the maintenance of blood pressure and the prevention of pulmonary infection take precedence over other forms of treatment.

Experience in the past two years has shown that bemegride is of undoubted value in the treatment of severe barbiturate coma with profound respiratory depression or apnoea.

Its main value lies in its analeptic and respiratory stimulant effects which, with care in administration, can be maintained over long periods without ill-effects.

Another possible use of bemegride, which has not yet been fully investigated, is its use in terminating anaesthesia from short-acting barbiturates, when the patient's cooperation is desirable and a rapid return to consciousness is required.

I am indebted to the Editors of the *British Journal of Anaesthesia* for permission to reproduce fig. 3.

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EQUIPPING THE SURGERY

II.—DRESSINGS AND ANTISEPTICS

BY SIR HENEAGE OGILVIE, K.B.E., D.M., M.Ch., F.R.C.S.

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IN contrast to surgical instruments, which are equipment, dressings and antiseptics are expendable stores. The doctor can get those that he wants for any particular purpose from the chemist, and he requires to keep in his surgery only those most likely to be needed in an emergency.

DRESSINGS

The general purpose of a dressing is to protect a wound, or to apply medication to an open or a healing surface. The dressing appropriate to any lesion will depend upon its size, its site, and its nature.

First-aid dressings.—The name is used for a small dressing applied immediately to a minor breach of surface, a cut, prick, blister or small burn, or to the sutured incision of a small operation. First-aid dressings are supplied under that name by leading manufacturers, usually in boxes of assorted sizes.

DRESSINGS FOR LARGER LESIONS

A dressing must protect a wound from mechanical injury and from bacterial contamination. At the same time it must allow evaporation from the skin, and absorb any discharge, so that the surface is kept as dry as possible. Maceration of the skin by sweat or pus favours the multiplication of bacteria and prevents healing, whilst unabsorbed discharge becomes an albuminous track, leading from the surface of the dressing to the wound, that encourages the entry and growth of contaminant bacteria.

The dressing must be retained in contact with the lesion but yet allow movement of that part.

The standard dressing materials today are absorbent gauze, cotton-wool, and open weave bandages; all three are made from cotton fibre.

Surgical gauze is woven in a loose mesh. It is supplied in rolls, nine inches (23 cm.) wide, of eight ply or layers, but it is made up in the hospital, or supplied by the manufacturers, in squares or oblongs of various sizes and ply, either folded so that the cut edges are inturned, or stitched at the sides.

Cotton-wool is supplied in sheets, that are moderately compressed and put up in rolls which may be interleaved with paper. It is sold by weight and comes in various qualities. The best quality—B.P.C.—is the most absorbent, and should be used for dressings. The cheaper, so-called hospital, qualities serve for padding, and for an outer layer over better quality wool.

Bandages.—The most useful are the ordinary rolled white, open-weave,

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B.P.C. type, 3, 4, or 6 yards long (2.75, 3.5 or 5.5 metres), and 1, 2½, or 4 inches (2.5, 6.5, or 10 cm.) wide. Two other types are useful.

‘Kling’ bandages are of cotton, loosely woven with the individual fibres taking an undulating course. They are useful to secure dressings over parts of irregular contour such as the neck or the joints where the warmth, pressure, or cost of crêpe bandages is not desired.

Crêpe bandages are woven of crimped material that usually contains some wool. They have an elasticity that allows them to lie smoothly over a curved surface and to exert a steady pressure.

Adhesive plaster and bandage.—Where a dressing is to be kept in position for some time, some form of adhesive plaster or bandage is usually preferred. The adhesive substance, which has a rubber basis, is applied to a specially woven cloth which may be rigid or provide a certain amount of elasticity. The most useful type for fixing dressings is made with minute gaps or perforations in the adhesive layer, so that evaporation can take place through the plaster. Some patients are sensitive to rubber adhesive. For them plaster with a different basis can be obtained.

STERILITY OF DRESSINGS

Many dressings are sold as sterilized, but that means no more than that they have been through a sterilizing process. Nothing remains sterile unless it has been transferred directly from the sterilizer to a sealed packet impervious to air or moisture. Dressings that have been sterilized and kept in clean and dust-free surroundings, however, are unlikely to become contaminated with pathogenic organisms.

Manufacturers put up sterile packets of swabs, of gauze pads, of wool or of the dressing materials required for a minor operation or a single dressing. The practitioner will require a few of these for primary dressings. For most purposes portions cut from bulk materials with sterile instruments and handled under aseptic conditions can be used.

DRESSINGS FOR OPEN WOUNDS

The features of an open wound are that its base is covered with granulations and its edges are fringed with thin growing epithelium, both of which are easily damaged. Its surface discharges pus or serum which must be absorbed by the outer layers of the dressing.

Some non-stick material must be laid on the surface, but none of these is entirely satisfactory; either they stick a bit, or they are waterproof and cause maceration. The best substance is probably a fine gauze net impregnated with petroleum jelly: a preparation usually known as ‘tulle gras’. On this is laid gauze, plain or soaked in some medicament, which can be changed without removing the ‘tulle gras’ or injuring the granulations.

When the discharge is copious, the dressing must be covered with enough absorbent material to soak up the discharge and allow none of it to reach the outside surface. Best quality and sterilized wool need be used only for the

first layer. Afterwards cheaper wool, or cellulose tissue, which is cheap and highly absorbent, may be used.

FILM DRESSINGS

Quick-drying solutions, that leave a film of plastic material on the skin, have a limited use for dressing small wounds that are clean and dry. Such a preparation is 'nobecutane', which is supplied in tins with a spray nozzle. The advantages of such a dressing are that it is quickly applied, thin, barely visible, and comfortable. The disadvantage is that it is waterproof, and if applied to any but a small area it causes maceration.

ANTISEPTICS

Antiseptics are reagents that are lethal to bacteria, but harmful to a much lesser extent to human beings. In lesser concentration they can restrain the growth of bacteria without killing them. There are many types of antiseptics, acting in different ways, and suitable for different purposes. About the worst is Lister's original antiseptic, carbolic acid. The action of an antiseptic *in vitro* varies with concentration, with time and with temperature, and when used in the tissues its value is largely governed by its toxicity and its reaction with organic matter in the wound. The leading properties of the main varieties are as follows:—

(1) *Oxidizing agents*.—Nascent oxygen combines with any organic matter, and is not selective for bacteria. The chief value of hydrogen peroxide lies in the mechanical cleansing of a sloughing wound.

(2) *Halogens*.—Chlorine and iodine are rapidly bactericidal in extreme dilution. Their disadvantage is that they combine with any organic matter and that they are occasionally irritating to tissue.

Chlorine is usually employed as a solution of hypochlorite (eusol, Dakin's solution). Chlorine is also added to coal-tar derivatives such as 'dettol'. Iodine is usually used as a 2½ per cent. solution in spirit. It is the best antiseptic for sterilizing the skin. Iodoform (CHI_3) has a wonderful 'antiseptic smell', but is entirely useless.

(3) *Heavy metals (mercury, copper, silver, zinc)*.—These have little use in surgery, owing to their toxicity and their vivid colouring. Mercuric skin sterilizers, 'metaphen', thiomersal ('merthiolate'), and mercurochrome, owe their appeal to their attractive colour rather than their bactericidal efficiency.

(4) *Alcohols*.—The only one in common use, ethyl alcohol, owes its popularity largely to its universal availability, its cleansing powers, and its ability to dissolve many other substances such as iodine. It coagulates proteins, and is therefore ineffective in a wound, in spite of its use for that purpose by the Good Samaritan. It is chiefly used to sterilize the skin, and glass and steel instruments. The optimum bactericidal concentration is 70 per cent.

(5) *Coal tar derivatives*.—Of these, phenol is almost useless. The cresols are used, usually with soap, for large-scale disinfection of bedding and furniture. Tar acids are sold as proprietary disinfectants ('izal', 'cyllin') for

floors, drains and lavatories. Other antiseptics ('dettol') are cresols or xynolols with a chlorine atom added. The members of this group act fairly rapidly, they are non-toxic, they do not coagulate proteins and act in the presence of serum or blood, and their efficiency is increased by soap.

(6) *Aniline dyes*.—Most aniline dyes are bactericidal in high dilutions, and their action is interfered with only moderately by blood and serum. Their bright colour and staining properties limit their use in practice. Bonney's blue (brilliant green and crystal violet) is favoured for sterilizing the vagina. Gentian violet is the best antiseptic for staphylococcal infections of the face severe enough to justify temporary social ostracism.

(7) *Acridine dyes*.—The members of this group (acriflavine, euflavine, proflavine, 'rivanol') have been popular since the 1914-18 War. They disinfect in dilutions of 0.2 per cent. and are bacteriostatic in dilutions up to 0.0001 per cent. They are, for practical purposes, non-toxic to the tissues, and their activity is hardly interfered with by the presence of blood or serum. They are particularly active against *Streptococcus pyogenes*.

(8) *The newer antiseptics*.—*Cetrimide* ('cetavlon') is a derivative of ammonium bromide, and is a detergent, much favoured for cleansing and sterilizing the skin. It is effective against streptococci and staphylococci, and relatively non-toxic.

Chlorhexidine ('hibitane') is a new antiseptic, the chemical formula of which is bis-*p*-chlorophenyl diguanidohexane. It can kill streptococci *in vitro* in a dilution of 1/10,000,000. It has been favourably reported on in gynaecological practice by Calman and Murray (*Brit. med. J.*, 1956, **ii**, 200).

SUGGESTED EQUIPMENT FOR THE SURGERY

As pointed out earlier, anything that may be needed in the way of dressings and antiseptics can usually be obtained at short notice from the chemist, and the doctor need keep no more than a skeleton equipment in his surgery. The following are suggested as meeting ordinary requirements.

(1) *First-aid dressings*

A 'factory outfit' of mixed sizes.

(2) *Sterile dressings*

- (a) A few packets of gauze pads, 4 x 4 inches (10 x 10 cm.) sterilized and in a sealed envelope.

A few 'multiple pack dressings' for first-aid, containing gauze, wool and bandages. These are put up by the manufacturing firms for use in the first-aid department of factories, according to the specification contained in the Drug Tariff issued by the Ministry of Health.

(b) *Ex-Army stores*

First Field Dressing (small).

Shell dressing (large). If obtainable from a disposal unit, these are useful for any kind of dressing. They contain a pad of wool covered with gauze, and a bandage in an impervious cotton

envelope. They were sterile when issued and can be sterilized again.

(3) *Stock dressings*

Gauze.—Packets of absorbent gauze, 3 yards by 36 inches (2.75 x 0.9 metre).

Wool.—First quality absorbent wool
Second quality wool
Cellulose tissue. } These are sold by weight.

Bandages.—*Open weave cotton*, 6 yards (5.5 metres) by 1 inch (2.5 cm.), 2½ inches (6.3 cm.) and 4 inches (10 cm.).

'Kling' bandages, 6 yards (5.5 metres) by 4 inches (10 cm.) and 6 inches (15.25 cm.).

Crêpe bandages, 6 yards (5.5 metres) by 2½ inches (6.3 cm.) and 4 inches (10 cm.).

(4) *'Tulle gras'*—one tin.

(5) *'Nobecutane'*—one spray tin.

(6) *Antiseptics*

(a) Surgical or methylated spirit—1 quart (1 litre).

(b) Tincture of iodine.

(c) *'Dettol'*.

(d) Tablets of acriflavine, for preparing 1/1000 solution.

(e) Chlorhexidine, 1/200 solution in 70 per cent. spirit, for keeping knives, scissors and needles.

Hydrogen peroxide and eusol, for dressing septic wounds, will be ordered as required.

REVISION CORNER

SNUFFLES

THE term 'snuffles', like some other conditions, such as 'wind', is more often used by mothers and midwives than by doctors. Surprisingly, most modern textbooks of pædiatrics make no mention of it except to state that snuffles is commonly a manifestation of congenital syphilis—a rare disease to-day.

ETIOLOGY

Snuffles is the audible effect of air passing through nasal passages partially obstructed by the secretion of mucus, which causes a bubbling sound. In mild degree this is quite common, and usually starts in the first week or two of life: sometimes the mother states that her infant was 'born with a cold'. The intensity and duration of the condition are variable, but in most cases a short mild course is seen. Occasionally snuffles may persist for a

year or more. There is no seasonal variation and no sex preference. The question whether the nasal obstruction is due to infection or to the secretion of excess mucus due to some other cause such as irritation, is not easy to answer.

The usual benign course, sometimes rather prolonged, and without any effect on the general health, suggests that the majority of instances are primarily non-infective, although secondary infection may occur at any time, and some babies clearly suffer from purulent rhinitis from the onset. These latter often have a clear history of contact with an adult in the household suffering from a respiratory infection. It would be better to regard such children as examples of infection who should be investigated and treated accordingly, and to reserve the term snuffles for the former group, in whom possibly some simple mechanical action, such as a sudden change of temperature, may cause a reaction in the nasal mucosa leading to an excess of mucus production, sufficient to cause symptoms only in small nasal passages. There is no evidence that allergy plays any part in the snuffles of infancy. In this connexion it should be noted that the infant's nose is more turned up than that of older people, so that foreign particles may enter more readily. Also, as the entrance is narrow, crusts may easily form and block the airway. Added to this, the choanæ, which cut off the nasal passages from the pharynx, are very small. The narrower nasal airway in premature infants doubtless accounts for the frequent occurrence of snuffles in these babies. For the same reason, a high incidence is seen in mongolism.

The nasal obstruction consequent to the condition has undesirable effects. The infant has great difficulty in breathing through the mouth, particularly for the first two to three weeks of life, as the tongue seems to act as a one-way valve which prevents air from passing from the mouth into the glottis. The greater the degree of nasal obstruction, the more likely is feeding difficulty to arise. This leads to refusal of food, choking and sometimes regurgitation with the risk of inhalation of vomit.

An infant with excessive nasal secretion rarely has much nasal discharge. The fact that the child spends most of his time recumbent means that secretions pass backwards into the nasopharynx, and may partly account for the alleged rarity of colds in small babies. In the usual case such discharge as there is is watery, but it may be too thick to appear.

Once established, snuffles leads to mouth-breathing which may be persistent. As a result the physiological functions of the nose are unused and the unmoistened, unfiltered air may set up pharyngeal irritation with subsequent infection and hypertrophy of the pharyngeal lymphoid tissue. Perhaps the development of 'adenoids' in infants may be assisted in this way and there is always the risk of nasal deformity developing in a long-standing case of nasal blockage.

Whether these children are more prone to pulmonary infection is uncertain—probably not, unless secondary nasal infection has taken place.

Conjunctivitis, in the form of the familiar 'sticky eye', is quite a common accompaniment.

DIAGNOSIS

This is usually simple, but *foreign bodies*, usually in the form of strands of cotton-wool, should be looked for. *Congenital choanal atresia* is exceedingly rare and affected infants appear very ill from anoxia if the atresia is bilateral. The successful passage of a rubber catheter through the nose into the nasopharynx will exclude this abnormality.

Œsophageal atresia with tracheo-œsophageal fistula, in which the œsophagus distal to the atresia communicates with the trachea, should be detected soon after birth. This is important, as the first feed will cause choking and vomiting with probable inhalation of the vomit. The abnormality should be suspected by the presence of *froth round the nostrils and mouth*. Oral secretions cannot be swallowed, so, mixed with air, they appear at nose and mouth, producing this characteristic sign in addition to snuffles. Failure to pass a catheter into the stomach will confirm the diagnosis.

Syphilitic snuffles is extremely rare nowadays. It does not generally appear until about the third week of life, and the discharge is profuse, purulent and blood-stained. Other signs of congenital syphilis will be present.

Cleft palate is commonly associated with snuffles and when, rarely, this is associated with maldevelopment of the mandible (Robin's syndrome), the condition is particularly troublesome. In this syndrome the poorly supported tongue tends to fall back and block the glottis.

Laryngeal stridor should be differentiated easily by the typical crowing sound on inspiration. The cause of this is an abnormally soft and folded 'infantile' larynx and the stridor generally disappears by the second year. Sometimes snuffles and congenital laryngeal stridor coexist in the same patient.

TREATMENT

When there is definite purulent discharge, a nasal swab should be taken to determine the causative organism and its sensitivity to the various antibiotics. In the usual, non-purulent case, the nasal airway should be kept clear, to avoid the evils of mouth-breathing. Cleansing the nose with cotton-wool is of doubtful value and may be dangerous, so when obstruction is marked, nasal drops may be tried. These should always be made up in isotonic solutions. Oily preparations should never be used owing to the risk of the development of lipoid pneumonia. Ephedrine, 0.5 per cent. in normal saline, may be tried; a drop in each nostril, three to four times daily, for a few days at a time. Perhaps the most important point of all is to try to establish nasal breathing in the more protracted cases by showing

the mother how to occlude the mouth manually for gradually increasing periods.

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BALDNESS

Alopecia in its different forms is not a simple problem, for the etiology ranges from hair-pulling to endogenous toxic agents, and hair growth is influenced by genetic, nutritional, endocrine and nervous factors. Diagnostically, it must be decided first whether there is accompanying atrophy or scarring. Thus alopecias can be classified broadly into cicatricial and non-cicatricial groups.

CICATRICAL ALOPECIAS

Circumscribed baldness may result from a wound, burn or caustic agent, or from local disease of sufficient depth to involve the hair follicles. The scalp is left smooth, shiny, waxy or wrinkled, and the follicular orifices have disappeared. Cicatricial alopecia follows destructive processes such as rodent ulcer, lupus vulgaris, tertiary syphilides, or severe sepsis of the pilosebaceous apparatus, such as carbuncle, and pitted scars remain after varicella, variola and zoster. In general, folliculitis and other coccal infections leave characteristic round bald spots on which the hair eventually regrows, although sometimes only after some months. Likewise, except for favus and suppurative ringworm (*herion celsi*), tinea capitis does not produce lasting baldness, although in the past the treatment sometimes did, and damage by x-ray epilation resulted in many cases of cicatricial alopecia. Nowadays, however, in expert hands and with accurate means of measuring x-ray dosage such a risk is practically non-existent.

The scalp may be the site of various chronic skin diseases which end in atrophy, such as scleroderma, lupus erythematosus and lichen plano-pilaris, and there is a supposedly 'essential' cicatricial disease of the scalp known as *pseudopelade* of Brocq, which is characterized by smooth, waxy, bald areas tending to coalesce in an irregular pattern and studded with occasional clumps of hairs. This, however, is now regarded as a doubtful entity.

Once the hair follicles have been destroyed for any reason the baldness is permanent and no treatment is of any avail.

NON-CICATRICAL ALOPECIAS

The health of a patient is often reflected in the condition of his hair and a chronic general disease may cause a progressive alopecia. The function of the hair-follicles, however, can be inhibited suddenly, as may the growth of the nails, by a severe constitutional upset or acute infective illness (*symptomatic alopecia*). Thus, diffuse hair-fall, occasionally universal, may be a sequel to childbirth, operations, typhoid fever, erysipelas, influenza (as in the 1918 pandemic) and so on. When this happens it is almost

invariably nine weeks after, and the hair comes out with alarming rapidity. Complete regrowth, however, is the rule, no special treatment is necessary and the patient can be reassured. The alopecia of secondary syphilis, occurring from three to fifteen months after infection, is of similar toxic origin but has a more insidious onset, the distribution is patchy and the denuded areas (unlike alopecia areata) are not completely bald but have a 'moth-eaten' look. The hair recovers in due course.

'Idiopathic' *premature alopecia*, which, like senile alopecia, is far more common in men than women, usually begins before the twenty-fifth year with a slow symmetrical recession at the temples and progresses inexorably, leaving in some the effect of the tonsure and in others a vestigial tuft in front, the hair at the back and sides remaining relatively thick. A hereditary predisposition is traceable in many cases but this must be combined with androgenic stimulation and the etiology is far from clear. Pityriasis capitis has been traditionally blamed for premature baldness (*alopecia pityroides*) but the relationship is difficult to assess. Dandruff, however, if present, requires persistent local treatment; for instance, with sulphur and salicylic acid preparations or selenium sulphide shampoo.

Marginal partial alopecia in women affecting just within the fronto-lateral hair-line is generally due to repeated traction on the hair-roots by metal haircurlers and grips, combined often with over-zealous scalp massage and brushing in an upward and backward direction with a stiff hairbrush. Constant traumatization of this kind seems to cause lasting damage to the hair-follicles resulting in a failure of the hair to regrow even when the procedures are stopped. In over-anxious women, usually of middle age, who are worried or have feelings of insecurity, there is a tendency to become obsessional about their hair, imagining it to be coming out 'in handfuls', and it is sometimes difficult to convince them that they are not about to go bald at any moment.

Children are not infrequently found to have linear, ragged or bizarre-shaped bald areas, possibly suggestive of alopecia areata or ringworm, which are simply due to hair-pulling, either through nervous habit or by another child in play. In *trichotillomania*, a form of neurotic tic, there is an uncontrollable impulse to pull the hair out.

ALOPECIA AREATA

Circumscribed alopecia without atrophy generally means alopecia areata. The patches are sharply annular, completely bald and often have short hairs in the periphery which are darker and thicker at their distal ends, resembling 'exclamation marks'. These are of diagnostic value but also indicate that the function of the hair follicles is still deranged and that further extension is likely.

Alopecia areata in children is sometimes mistaken for non-inflammatory ringworm, but ringworm patches are covered with fine scales and stumps of greyish broken hairs. The diagnosis can be established quickly by

examining the scalp under Wood's light in a dark room, when the infected hairs in common ringworm show a green fluorescence.

The mechanism of alopecia areata is unknown. There is a familial tendency in some cases and in many a relationship with emotional disturbance, the commonest precipitating cause (about 25 per cent. of patients) being mental shock or acute anxiety. Often the regrowing hair is unpigmented, suggesting a connexion with *vitiligo*, and the two disorders are sometimes combined.

It is doubtful whether treatment makes any difference: e.g. high frequency, 'vibro-massage', ultra-violet light and other procedures beloved of 'scalp experts', but the patient must be told that spontaneous recovery occurs in more than 99 per cent. of cases. If over-anxious he should receive phenobarbitone, $\frac{1}{2}$ grain (30 mg.), or amylobarbitone, $\frac{3}{4}$ grain (50 mg.), twice daily, and tension may be reduced with meprobamate, 400 mg., three times a day. Peripheral vasodilators have been tried but it has been shown recently that β -pyridyl carbinol ('*ronicol*') has no effect on the growth of hair in alopecia areata, male baldness or diffuse hair-thinning in women. Cortisone by mouth has caused regrowth of hair in cases of alopecia areata, totalis and universalis, but the hair comes out again when therapy is stopped and the dosage necessary is far too dangerous for long-term use. There may, however, be a case for the short-term administration of steroids in a rapidly extending alopecia.

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NOTES AND QUERIES

Winter Resorts for Asthma

QUERY.—Could you please recommend a resort to which I could send a patient with bad asthma for, say, a month in winter?

REPLY.—To recommend a suitable holiday resort for an asthmatic in winter it is necessary to have some knowledge of the underlying factors causing attacks. When emotional factors are playing a part, the choice of a holiday companion is perhaps more important than the locality. If allergy predominates, clear air and dust-free bedrooms are important, and the Swiss mountains probably offer the most favourable conditions: for these cases the Mediterranean islands, and the warm coastal resorts of Southern England in Somerset and Devon appear to be unfavourable. If low-grade infection is playing an important part, the south coast of France, Bournemouth or the Bahamas offer good prospects of recovery. Travelling is best done by air both because of the freedom from effort and discomfort, and because the risk of acquiring fresh infections

while travelling is minimized. Air travel is in itself good for most cases of asthma.

R. S. BRUCE PEARSON, D.M., F.R.C.P.

Tetanus Immunization

QUERY.—I should be grateful for the following information:—

(1) Is there any contraindication to the use of tetanus toxoid, or danger in its use?

(2) In particular are (a) previous sensitivity-reaction to A.T.S., (b) an allergic history such as asthma or urticaria, indications to give tetanus toxoid (rather than contraindications)?

(3) After initial immunization with toxoid in either infants (perhaps with diphtheria toxoid and whooping-cough vaccine) or adults what should be the programme of reinoculation?

REPLY.—(1) There is no contraindication to giving tetanus toxoid, as reactions following its use are so infrequent and mild.

(2) A history of serum allergy, asthma or urticaria is an indication to immunize actively with toxoid and thus to obviate the emergency

use of antitoxic serum for prophylaxis or therapy. Allergic patients should receive, purely as a precautionary measure, a reduced dose (e.g. 0.1 ml.) of toxoid, followed after some hours, or the next day, by the ordinary dose of 1 ml. if no symptoms have occurred. Both these doses are given deep subcutaneously or intramuscularly. The subcutaneous injection of 0.5 ml. of 1:1000 solution of adrenaline, repeated if necessary, may confidently be expected to control any allergic reaction—a most unlikely event with toxoid, even in a patient with a history of severe asthma.

(3) Reinoculation of tetanus toxoid is advisable after 6 to 9 months, and thereafter at intervals of four or five years. It is not yet known how long one should continue to give boosting doses at these wide intervals in order to ensure life-long protection. An additional boosting dose of tetanus toxoid may be needed after a dirty cut, unless a full primary course, plus adequate boosting dose, have been given and the last injection has been less than, say, eighteen months before. In this connexion patients or their parents must be asked to safeguard a permanent record card of inoculations, which, so far as possible, must be readily accessible when required.

H. J. PARISH, M.D., F.R.C.P.E.D.

Virus Immunity

QUERY.—In the case of the various viral infectious diseases of childhood, e.g. measles.

(1) During an epidemic do immune adults carry the virus and should they be regarded as possibly infectious?

(2) Are children incubating the disease infectious during the whole quarantine period?

(3) At non-epidemic times is there any of the virus at large in the community or is it completely absent?

REPLY.—It is not possible to give precise answers to these important and interesting questions. Of the many difficulties which preclude a complete picture of the behaviour of these viruses, mention must be made of the failure until recently to grow in the laboratory those causing measles, German measles and chickenpox. The possibility of demonstrating them by culture in human or monkey tissue has now been realized but even with those which multiply readily in fertile eggs (e.g. mumps, influenza, smallpox) the chance of detecting a very small amount in the throat of a healthy person must be slender. Such answers as can be given to general questions of this sort must therefore depend upon inference and analogy rather than objective support.

(1) The lasting immunity which results from these virus infections is believed by many to

depend upon a continued but quiescent infection by the causal agent. There is evidence that infection, and immunity, may be acquired without the development of clinical illness. Immune adults may therefore be persistent carriers of virus regardless of epidemic incidence of the disease, but it is probable that this usually involves no risk to others since the virus is present in small amount in deeply sited organs—perhaps in the spleen or bone marrow. They are, in other words, closed carriers. With viruses such as measles or mumps, which do not spread immunologically, it seems very unlikely that immune adults would support even a transient upper respiratory infection transmissible to susceptible individuals but infection of the immune may take a subclinical form, and prove infectious to others. Mechanical transfer through contamination of hands and clothing is a quite different possibility and depends upon the amount of virus discharged from a patient and its ability to survive outside the body: knowledge of this property is mainly very incomplete.

(2) The portal of entry in most of these viral infections is respiratory. At first the virus multiplies in the superficial cells of the epithelium. During incubation an increasing amount of virus is being built up largely in other tissues. Presumably some of the cells lining the upper respiratory tract are infected throughout the incubation phase but the amount on the mucous surface is then probably very small. Together with the absence of respiratory symptoms at that time, must limit considerably the chances of transmission to others—by contact with the state of affairs at the start of the clinical illness. Although the incubation period of 'pharyngoconjunctival fever' is only about 10 days, it is noteworthy that recent observations (Roden, A. T., Pereira, H. G., and Chapronis, Donna, *Lancet*, 1956, 2, 592) on human volunteers showed that A.P.C. virus could not be demonstrated in garglings collected two days after experimental infection of the throat. Some were positive at 4 and 6 days.

(3) Since virus is not regenerated to start a new epidemic, it must be 'at large' in a restricted way in non-epidemic times. Its presence may be revealed by the occurrence intermittently of a few cases or concealed in the minor forms of illness which escape recognition.

PROFESSOR C. F. BARWELL, M.D.

Endocrine Imbalance and Homosexuality

QUERY.—Is there any known relationship between homosexuality and endocrine function? Is there any biochemical means of measuring such hormonal imbalance and are there any authoritative literature on the subject?

REPLY.—Although the opinion was firmly expressed by Krafft-Ebing (1892) that homosexuality, and various other disorders of sexual behaviour, are due to endocrine imbalance, whilst many others writing after him have held the same views, it can be stated quite categorically that no convincing demonstrations of such hormonal imbalance have been forthcoming. Moreover, many students of the subject have taken precisely the opposite view, namely, that homosexuality, and other disorders of sexual behaviour, are the results not of endocrine disturbance, but of psychological maladjustments. The question was discussed in an article in *The Practitioner* by Swyer (1954), to which the reader is referred for further reference.

The most recent contribution to the literature on hormone excretion studies in patients with anomalies of sexual behaviour has been made by Garrone and Mutrux (1956). These authors have demonstrated convincingly that the urinary steroid excretion (they determined total 17-ketosteroids and their different fractions, 3- α -steroids, formaldehydogenic corticoids, 'total corticoids' and 17, 21 - dihydroxy - 20 - keto-steroids) in a group of 50 patients was no different from that of normal men of comparable ages. There seems no reason to doubt that homosexuality has, in general, no endocrine basis. The one possible exception to this conclusion is the rare case of passive homosexuality in a eunuchoid; in such cases alone may hormone therapy bring about a reversal of sexual outlook.

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G. I. M. SWYER, D.M., M.R.C.P.

Care of Children in West Africa

QUERY.—A patient, whose husband is thinking of applying for a post in the Gold Coast, has

asked my advice on the following points and I should be grateful for guidance and information.

(1) She has at present two children, aged two years and three months, and is anxious to know whether the climate would affect them disadvantageously over a period of years.

(2) Is it possible to get adequate supplies of fresh fruit, milk, and vegetables?

(3) She is Rh-negative and her husband is Rh-positive. Whilst no antibodies were found in her second pregnancy, she wants to know whether if this did happen in a subsequent pregnancy there would be facilities for exchange transfusion, should this be necessary? Also whether as a general rule Europeans are advised to return to this country for confinements?

REPLY.—It can be confidently asserted that climate *per se* does not adversely affect the growth and development of children. Many thousands of European children have been brought up in the tropics, including West Africa, and have suffered no ill-effects. In West Africa educational facilities are inadequate for European children over the age of 10 years; at that age it is usual to send them to school in this country.

Fresh fruit and vegetables are in plentiful supply throughout West Africa, but fresh milk can only be obtained in certain localities. Dried or evaporated milk is usually used as a substitute and the makers' claims regarding the excellence of these products are fully borne out by experience of those who use them in West Africa.

It is not the general rule for Europeans to return to Europe from West Africa for confinements, although a considerable proportion of them do so. If there is any question of an exchange transfusion being necessary, it is strongly recommended that arrangements should be made for the confinement in the United Kingdom. The technique of exchange transfusion is not yet in use in West Africa.

PROFESSOR A. W. WOODRUFF, M.D., F.R.C.P.

PRACTICAL NOTES

Eczema of the Eyelids

DURING the five-year period, 1951-55, 238 cases of eczema of the eyelid were seen in the dermatological department of Moorfields Hospital, and these constituted 20% of the total cases seen. In an analysis of these cases, Peter Borrie (*British Journal of Ophthalmology*, December 1956, 40, 742) draws attention to the fact that 68 of them (29% of the entire series) were cases of dermatitis medicamentosa. Nearly two-thirds of this group (42) were due to penicillin (in the form of cream rather than drops) or sulpha-

cetamide. This is described as 'being in keeping with dermatological experience, local penicillin and sulphonamide therapy having long been abandoned'. Treatment consisted of bland therapy. The few cases with gross secondary infection were treated with 0.5% neomycin ointment. Neomycin is 'recommended for the routine treatment of staphylococcal infection of the eyelids. It is quite as effective as the other antibiotics, very rarely sensitizes, and is never used systemically, so that if resistant strains of bacteria result from its use this will not affect

future systemic antibiotic treatment'. The third largest group was that due to contact dermatitis. Of the 47 cases in this group, five were due to cosmetics (including one due to nail varnish and one due to a man using his wife's face cream). Treatment in this group consisted of removing the causative factor, and local application of 0.5 to 1% hydrocortisone ointment. In the presence of secondary infection, this was replaced by a mixture of 1% hydrocortisone and 0.5% neomycin ointments. There were 12 cases of suspender dermatitis (nickel sensitivity). None of these associated the eyelid condition with that under the brassière, suspender or buckle. Here again the local application of hydrocortisone ointment proved beneficial. The largest group was that of infective dermatitis (77 cases). Treatment consisted of neomycin ointment followed by, or combined with, hydrocortisone ointment. Hydrocortisone ointment also proved useful in the treatment of the 14 cases of neurodermatitis.

Cancer and Achlorhydria

'It seems not unreasonable to accept the presumptive conclusion that in persons with low gastric acidity or pernicious anaemia the probability of occurrence of gastric cancer is greater than in persons with normal acidity'. Such is the conclusion of J. Berkson, M. W. Comfort and H. R. Butt (*Proceedings of the Staff Meetings of The Mayo Clinic*, October 31, 1956, 31, 583) based upon a 15-year follow-up of 1,058 patients with achlorhydria, 221 of whom had also pernicious anaemia, and whose ages ranged from 30 to 59 years. Whilst the 15-year survival rate was little different from the expected rate, except in the case of males with pernicious anaemia, the number of deaths from carcinoma of the stomach was appreciably higher in the achlorhydric group. The number of deaths from this cause was 26, compared with an expected number of 4.5. In the case of the patients with achlorhydria without pernicious anaemia the number of deaths was 18, compared with an expected number of 3.4, whilst in the case of those with pernicious anaemia the number of deaths was 8, compared with an expected number of 1.1. The recorded number of deaths from carcinoma of the stomach comprised 13% of the total deaths, whereas the expected rate was only 2.3%.

Recording Blood Pressure

It is always recommended that in recording the blood pressure the cuff should be applied evenly and snugly around the arm. If the cuff is applied loosely an erroneous reading will be obtained. W. F. Nuessle (*American Heart Journal*, December 1956, 52, 905) has investi-

gated the problem in 100 individuals, in whom he recorded the brachial blood pressure with a clip-on cuff applied tightly, and then with the cuff loosened so that its circumference was extended 3.1 cm. He found that in 94 instances higher readings were obtained with the loose cuff than with the tight cuff. The mean increase was 8.1 mm. Hg systolic, and 9.3 mm. Hg diastolic. The difference between the two readings was greater in individuals of average or heavy build (9.8 mm. Hg systolic, and 11.5 mm. Hg diastolic) than in lean persons (5.4 mm. Hg systolic, and 6.5 mm. Hg diastolic). It is suggested that a loose cuff gives high readings because of the central ballooning of the bag which exerts the pressure effect of a narrow cuff, and it is known that a narrow cuff gives abnormally high readings.

Essential Hypertension in Infancy and Childhood

TAKING as their criterion a persistent systolic blood pressure of 130 mm. Hg and a diastolic pressure of 90 mm. Hg as the upper limits of normal, R. J. Haggerty *et al.* (*American Journal of Diseases of Children*, December 1956, 92, 535) give an analysis of nine cases of essential hypertension in children aged 14 years or less. There were five boys and four girls, and the age at discovery of the hypertension ranged from 7 months to 13½ years. A family history of hypertension was present in five instances. The five patients with severe hypertension (160/110 mm. Hg or above) ranged in age from 7 months to 12 years, all had symptoms attributable to their hypertension and all showed evidence of secondary vascular changes. In only one was there a family history of hypertension. The remaining four patients were all aged 9 years or over when the hypertension was discovered, and all were 'singularly symptom free'. All had 'a strong family history of essential hypertension'. Stress is laid upon the importance of excluding other causes of hypertension, such as renal disease, phaeochromocytoma and coarctation of the aorta, before making a diagnosis of essential hypertension in children.

The basis of therapy has been a barbiturate weight reduction in the obese, and superficial psychotherapy. Restriction of physical activity has been found harmful rather than helpful, except in the presence of symptoms such as headache or dyspnoea, and participation in competitive games has been discouraged. The children with mild hypertension (under 160/110 mm. Hg) were given a Rauwolfia preparation starting off with either 0.1 to 0.25 mg. of reserpine, or 1 mg. of 'rauwiloid', thrice daily, and increasing the dose every two to three weeks.

until side-effects occurred. The dose was then reduced until side-effects disappeared, and administration continued indefinitely at this level. In those with severe hypertension the Rauwolfia was supplemented by hexamethonium. If this did not prove effective, sympathectomy was performed. This was done in four cases—with benefit in two instances.

Reducing Diets

THE following simple formula is given by R. J. Slonim Jr. (*Journal of the American Medical Association*, November 24, 1956, **162**, 1233) for calculating the caloric value of a reducing diet for a moderately sedentary adult:—

$$C = 11.4 (7H - 266 - 6L)$$

where C = calories per day; H = height in inches; L = desired loss of weight per month, in pounds.

The bases for this formula are the three following assumptions: (1) The 'ideal' weight for an individual may be calculated by a rule of 110 lb. (49.9 kg.) for a person 5 feet (152.4 cm.) tall, with 5 lb. (2.3 kg.) added for each additional inch. (2) A person who is mainly sedentary requires a daily dietary allowance of 35 calories per kg. body weight to maintain a constant weight. (3) If a person eats more than 35 calories per kg. of his ideal weight daily he will gain weight at the rate of 1 g. of fat + 1 g. of water for each 9 calories in excess. On these assumptions the ideal diet in calories per day is:—

$$35 \left[\frac{5(H - 60) + 110}{2.2} \right]$$

The pounds of fat and water lost per day are converted to calories lost per day by the equation:—

$$L \times 9 \times 1000$$

$$\frac{2.2 \times 2 \times 30}{2.2 \times 2 \times 30}$$

The difference between these two equations gives the required number of calories:—

$$C = 35 \left[\frac{5(H - 60) + 100}{2.2} \right] - \frac{L \times 9 \times 1000}{2.2 \times 2 \times 30}$$

This equation can be further simplified to that given at the beginning of this note. In his article Dr. Slonim includes a nomogram, based upon this formula, which simplifies the calculation of reducing diets still further.

Chlorpromazine and Agranulocytosis

CAREFUL clinical and laboratory observation of patients receiving chlorpromazine is essential to prevent occurrence of agranulocytosis', accord-

ing to G. Schick and J. Virks (*New England Journal of Medicine*, October 25, 1956, **255**, 798). This conclusion is based upon their experience with the drug since 1954 in over 700 mentally ill patients in hospital. During this time they have had 11 cases of obstructive jaundice due to chlorpromazine, one case of agranulocytosis (full details of which are given) and two patients in whom malaise, fever, sore throat with ulceration, and decrease of granulocytes in the peripheral blood appeared. In a review of the literature they have found reports of 21 cases of agranulocytosis associated with chlorpromazine therapy. All were females, and in all but two cases the daily dose did not exceed 320 mg. In all but one instance the drug was given orally. The duration of chlorpromazine therapy ranged from 18 to 67 days, with an average of 43 days. Eight of these cases were fatal, and three of these also had jaundice.

Myotatic Irritability

MYOTATIC irritability is 'dependent on the nutritional status of the patient, and is much more likely to be encountered in males', according to I. A. Short (*Scottish Medical Journal*, December 1956, **1**, 399). He investigated the phenomenon in 527 outpatients whom he classified into four groups according to their habitus: Group 1: obese or well covered. Group 2: average build—no evidence of loss of weight. Group 3: naturally thin—no evidence of loss of weight. Group 4: considerable loss of weight or emaciation. Of the 23 males in group 1, only three had myotatic irritability, compared with 22 of the 23 in group 4. Of the 40 females in group 1, none showed myotatic irritability, and only six of the 18 in group 4 did. Of the entire group of 242 females in the series, only eight showed the phenomenon, compared with 155 of the 285 males. It is suggested that the sign is absent principally where subcutaneous fat is plentiful, and that this may be due to masking of the contraction or to interference with the stimulus to the muscle fibres. This would explain the relative rarity of the phenomenon in women, as subcutaneous fat is much more plentiful in females than in males. In other words, the sign has no clinical significance, and the 'so-called association with pulmonary tuberculosis was merely due to the accompanying cachectic state'.

'Mondor's Disease'

IN reporting seven cases of subcutaneous phlebitis of the breast and chest wall, or Mondor's disease as it is sometimes known, P. A. Kaufman (*Annals of Surgery*, November 1956, **144**, 847) gives an account of the salient features of the

disease. It presents characteristically as a slightly tender subcutaneous cord, 15 to 25 cm. in length and 3 to 4 mm. in diameter. The veins most commonly involved are those situated on the anterolateral aspect of the upper portion of the breast, or in the region extending from the lower portion of the breast across the submammary fold towards the costal margin and epigastrium. The cause of the condition is not known. It often appears without any precipitating incident. Not infrequently the patient first notices a slightly tender strand on raising the arms. When associated with severe inspiratory pain it may occasionally produce actual dyspnoea. It occurs in young and middle-aged adults of both sexes, but is more common in women. The process is 'uniformly self-limiting' and usually subsides in a few weeks or months, although an indurated cord may persist for one or two years. There is no effective form of treatment. Antibiotics and anticoagulants have been used but without demonstrable effect. Biopsy should be performed only in those cases in which the possibility of some serious underlying condition, such as malignancy, arises. The prognosis is uniformly benign; no deaths or recurrences have been reported.

Tuberculosis in Cats and Dogs

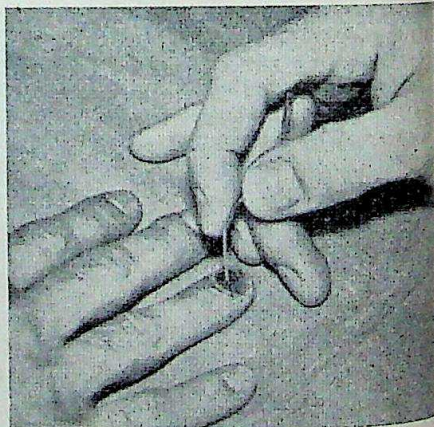
THE incidence of tuberculosis in cats is about 2%, according to S. F. J. Hodgman, of the Animal Health Trust Canine Research Station, Newmarket (*NAPT Bulletin*, 1956, 19, 205), but varies geographically, being largely dependent upon the prevalence of tubercle bacilli in the milk supply. They have a 'formidable resistance' to infection with the human and avian types of tubercle bacilli, but are readily susceptible to the bovine type. Once established in the cat, the disease is widely disseminated and highly destructive. Although there is lack of proved instances of tuberculosis being communicated from the cat to man, the view is expressed that 'the tuberculous cat must be considered as a potential source of infection, especially dangerous to children'. The only safe course, 'and often the most merciful', is to have the tuberculous cat destroyed. The incidence of the disease in dogs is not known. They may be infected by a member of the family with which they live or by contaminated food. Diagnosis may be difficult, but the suggestive symptoms are cough of variable duration and a steady loss of weight. Any dog with such symptoms should be seen by a veterinary surgeon. As in the case of the cat, it is recommended that the infected dog should be destroyed.

In reviewing the general situation, the view is expressed that 'the incidence of tuberculosis amongst both dogs and cats is too low to warrant

any decline in the popularity of these useful almost universal pets'. Although the dog population of the British Isles is numbered in millions, in the course of thirty years of general veterinary practice in small animals the author has only encountered two cases of tuberculosis in the dog. Both were the result of infection acquired by the animal from a human member of the household.

Treatment of Subungual Hæmatoma

A SIMPLE, relatively painless method of dealing with a subungual hæmatoma is described by J. K. Donahue (*GP*, December 1956, 14, 114). Strict asepsis is essential, but no anaesthesia is required. A paper clip is unfolded and bent into a shape that is easy to hold. The free end is heated in the flame of an alcohol lamp (a cigarette lighter has been used) until it glows. It is then allowed to cool momentarily. The



the glow disappears it is pushed vertically, with steady pressure, through the nail into the subungual hæmatoma. This is immediately evacuated and the pain is relieved. Two points are stressed. The first is the importance of prompt cooling of the end of the clip. If it is allowed to cool while still glowing 'there is a tendency to incinerate the blood which causes obstruction of the opening'. The second is that steps must be taken to ensure that the tip of the clip is not pushed through so forcibly that it penetrates through the painless hæmatoma into the sensitive nail bed. This can be prevented by bracing the hand as shown in the accompanying illustration. Following the puncture, a piece of tape is placed over the opening for twenty-four hours. The nail is usually normal but the opening persists until nail growth allows it to be cut off 'in the usual procedure of manicure'.

REVIEWS OF BOOKS

Handbook on Poliomyelitis. BY JOSEPH TRUETA, M.D., F.R.C.S., A. B. KINNIER WILSON, M.B., M.R.C.P., D.P.M., and MARGARET AGERHOLM, B.M., B.Ch. Oxford: Blackwell Scientific Publications, 1956. Pp. vi and 139. Illustrations 31. Price 20s.

THIS small book on the diagnosis and practical management of poliomyelitis is written particularly for the general practitioner and the doctor in the infectious disease hospital. Most books dealing mainly with the acute stage of poliomyelitis have an epidemiological and clinical slant. So has this one but it is probably unique in the refreshing anatomico-pathological approach which pervades all its teaching, owing doubtless to the influence of its principal author. That distinguished orthopaedic surgeon and original thinker, in close touch with the problems of management of the acute stage, has left his mark here, and the new light shed on old problems is a stimulus to the practising physician. Examples are the clear descriptions of the motor unit, of the mechanics of the respiratory tract, of applied respiratory physiology, and of the principles which should govern the work of physiotherapists and others during recovery and permanent disability.

Another important point is the conservative view taken of tracheotomy. It is for occasional use only, and its disadvantages, here clearly set out, should be ever present in the minds of those responsible for the management of respiratory complications. Muscle charting and training, rehabilitation, the technique of the heated pool and cognate subjects are dealt with in masterly fashion.

There are very few grounds for criticism. The negative aspects of gamma globulin prophylaxis and of quarantine for contacts are understated or omitted. The exceedingly efficient new intermittent positive-negative pressure respirators, with their useful attachments for suction, alveolar-air sampling and spirometry, are perhaps too recent developments to have been dealt with at the time of writing.

Pediatrics. Edited by DONALD PATERSON, M.D., and JOHN FERGUSON MCCREARY, M.D. Philadelphia: J. B. Lippincott Co.; London: Pitman Medical Publishing Co. Ltd., 1956. Pp. xvi and 654. Figures 192. Price £5 10s.

PROFESSORS PATERSON AND MCCREARY with their collaborators, all but one now working in Canada, have done for paediatrics in that country what 'Garrod, Batten and Thursfield'

did in Great Britain over forty years ago. By using double columns and frequent passages in small print they have packed a vast amount into just over six hundred pages of text. It is said to be intended for those in general practice with the stress on diagnosis and treatment, but in fact it goes well beyond this in detail. Sampling shows a remarkable evenness of style, indicating skilful editing, and there are several useful appendices on drugs, normal values and diet. The publishers' blurb on the 'up-to-the-minute' nature of the work provokes the reviewer to find fault and therefore it must be stated that there are improved methods of collecting urine from boy babies not involving a breakable test-tube and that there is no clinical account of hypercalcaemia. Denis Browne should have received credit for his views on the mechanical effects of malposition *in utero*.

Dermatology. BY DONALD M. PILLSBURY, M.D., D.Sc.(Hon.), WALTER B. SHELLEY, M.D., Ph.D., and ALBERT M. KLIGMAN, M.D., Ph.D. Philadelphia and London: W. B. Saunders Co., 1956. Pp. xix and 1331. Figures 564. Price £7 7s.

THIS newcomer to dermatological literature has one outstanding virtue. It differs from many other textbooks in that the three authors have recorded clearly and readably their own personal views and philosophies on all aspects of dermatology. It is no re-hash of older textbooks. In fact, it might be called 'Dermatology with the New Look'. Vague terms and obsolescent synonyms are omitted, to the relief, surely, of most readers. The authors state that 'at least a third of the terms ordinarily found in inclusive dermatological texts have escaped mention'. This has helped to provide more space for applied physiology, psychiatry, associated systemic findings, genetics, and other important subjects.

The work is rightly called 'dermatology', dealing as it does with the skin in health and disease. The five main sections deal with basic principles, allergy, diagnosis, therapy, and cutaneous medicine—a term which conveys well the desire to integrate dermatology with 'internal' medicine. Chapters on the fundamentals of cutaneous mycology and bacteriology provide up-to-date reviews on these topics. The chapter on hereditary cutaneous disorders contains an informative introduction on clinical genetics. In the preface, the authors state that they have 'found it impossible to maintain an attitude of consistent solemnity in respect of the subject matter in hand'. Presumably, these remarks refer to the use of cartoons to show the factorial

causation of such conditions as contact dermatitis, nummular dermatitis, seborrhœic dermatitis, and acne vulgaris. These cartoons are original and faintly amusing, but sometimes obscure. For example, the strato-cumulus cloud-like mass hovering over nummular dermatitis has the sinister appearance of an H-bomb spill-out but is presumably intended to show the fog of ignorance regarding the etiology of this condition.

This book is a first-class and authoritative source of knowledge whether the reader wants a single fact or a considered opinion on a broad topic.

Head Injuries and their Management. By FRANCIS ASHBURY ECHLIN, M.D., C.M., F.A.C.S. Philadelphia: J. B. Lippincott Co., 1956. London: Pitman Medical Publishing Co. Ltd., 1957. Pp. x and 127. Figures 10. Price 24s.

THE treatment of severe head injuries has suffered during the present century from a number of fashions regarding such matters as dehydration and when to operate. In these respects, this small book from the United States is thoroughly sane and practical, and will be found most useful by the general surgeon who deals with these cases. In the United States, however, these cases are evidently still being transported in the supine position, which is now thought to be undesirable owing to the danger of inhaling secretions or vomit.

Progress in Hematology, Vol. I. EDITED BY LEANDRO M. TOCANTINS, M.D. New York and London: Grune and Stratton Inc., 1956. Pp. ix and 336. Illustrated. Price \$9.75.

As indicated by the title this is a review of recent work in the field of blood diseases. It consists of sixteen chapters on various subjects, each written by different authors. With the exception of the British authors, Ungley and Thompson, who have written the first chapter entitled 'Gastric Intrinsic Factor and Vitamin B₁₂ Interrelationships', all the remaining contributors are American. A wide variety of topics is covered, including such subjects as parenteral iron therapy, radioactive phosphorus in the treatment of polycythæmia, thrombocytopenias, surgery of hæmophilia, fibrinogen deficiencies, and chemotherapy of leukæmia. The standard of writing and of production is excellent, and many of the chapters are illustrated with excellent graphs, diagrams, and photographs. Adequate bibliographies are appended to each chapter.

The book can confidently be recommended

to all who are interested in hæmatology but especially to those whose work lies in clinical applications, for the emphasis is on practical rather than the theoretical aspects of the subject. The physician having to deal with patients suffering from blood diseases will find this book a reliable and very readable source of information.

Interesting Cases and Pathological Considerations. BY F. PARKES WEBER, M.R.C.P., F.S.A. London: H. K. Lewis & Co. Ltd., 1956. Pp. iv and 77. Figures 5. Price 18s. 6d.

DR. Parkes Weber's name has stood for decades as a symbol, or even a synonym for a combination of a peerless clinical memory, a connoisseur's love of rare things and keen power of speculation. Anything from his vast store of knowledge which he commits to paper is read with avidity by those whose interests match his own, however much their ability lags behind. This latest book will be no disappointment: it is full of the type of information and scholarship which is pre-eminently his. Some of the articles have already appeared as original papers in scientific journals, an instance being 'The most Interesting Case' (*The Practitioner*, February 1956), but lose nothing in the re-reading. Others are quite new.

The syndrome to which Dr. Parkes Weber gave the name of Steiner Voerner he regards as being in all probability due to a serotonin-producing carcinoid tumour, and suspects that some cases of flushing, which have had regarded as examples of the auricular triphasic syndrome, had a similar origin. The chapter on 'A Portrait Medal of Paracelsus' gives a fascinating picture of the great 16th century physician, and, together with his 'numismatic suggestion', gives yet another example of the author's diverse interests and his ability to become an expert in many intellectual fields.

The Premarital Consultation. BY ABRAHAM STONE, M.D., and LENA LEVINE, M.D. New York and London: Grune and Stratton Inc., 1956. Pp. v and 91. Figures 11. Price \$3.

THE premarital examination as a branch of preventive medicine is relatively a modern development and one which has become more general in the United States than it is in Great Britain. This American book describes the conduct of such a consultation. A young engaged couple, John and Mary, are taken through the various stages of such a consultation. Sexual techniques and contraception are adequately described and the tone of the book

throughout both sympathetic and helpful. The reader is left in some doubt as to what should constitute a premarital examination. The authors are obviously not certain in their own minds as to whether certain tests, such as the male fertility test, should be undertaken before marriage, and their doubts are to some extent transmitted to the reader. Nevertheless, this little book should be read by all who are likely to advise and examine those about to be married. The list of marriage laws in the various States which forms an appendix makes fascinating reading and enables the British reader to get a glimpse of the varied communities which make up the United States.

Manual of Human Anatomy. By J. T. AITKEN, M.D., G. CAUSEY, M.B., F.R.C.S., J. JOSEPH, M.D., M.R.C.O.G., and J. Z. YOUNG, M.A., F.R.S. Edinburgh: E. & S. Livingstone Ltd, 1956. Vol. I: *Thorax and Upper Limb*, price 14s. Vol. II: *Head and Neck*, price 16s. Vol. III: *Lower Limbs*, price 12s. 6d.

DISCUSSIONS about the medical curriculum usually centre round the teaching of anatomy. It has been pretty generally agreed that the subject cannot be simplified and condensed, but many have urged that the teaching should be made more logical, and that instruction on the function of a part should be blended with the study of its form. This new work attempts to give expression to the modern outlook. Paragraphs indicating the function of parts come after the dissecting instructions, so that the study of the anatomy of the part is undertaken with some knowledge of its functional complications, and not as a mere exercise of memory. The authors advise that dissection should begin with the thorax, which is therefore described in the first part of volume I. The student thus becomes acquainted early with the heart and lungs, peripheral and autonomic nervous systems, all of which he will meet in the introductory courses in physiology. He also starts with the origin of the great vessels, whose further ramifications he will follow in later dissections.

Unlike many manuals, these volumes are really designed to be carried in the hands, and not in grubby hands at that. The covers are of tough and well-varnished cardboard, and, like telephone books, each volume is a distinctive colour. The pages, bound with wire rings through perforations, are designed to stay open and lie flat on a bench beside the dissector. The print is bold. The illustrations are intended to be studied with the text on the page opposite, and they are remarkably clear and free from

superfluous captions and arrows. Colour is used freely to give clarity.

These are admirable books. They will prove invaluable to the student starting on his two years' work in the dissecting room.

The Inquisitive Physician. By FRANCIS M. RACKEMANN, A.B., M.D. Cambridge, Massachusetts: Harvard University Press; London: Cumberlege, 1956. Pp. xi and 288. Illustrated. Price 40s.

THIS biography of George Richards Minot by his cousin, himself a distinguished alumnus of the Boston Medical School, scarcely does justice to the subject. The story of Minot's application to the treatment of pernicious anæmia of Whipple's experimental work on dogs is well known, but it would be difficult from this biography for anyone who happened to be ignorant of the story to be able to piece it together in a coherent manner. Indeed, the book is more accurately described as a family album of the Minot family, seen against the background of the Boston of the first half of the century. As such it presents an interesting picture of that select society which has contributed so much to the intellectual life of the United States. Minot was a Bostonian of the Bostonians. His life and activities began and ended there, and trips abroad, or even elsewhere in the United States, were made merely from a strong sense of duty. There is something rather charming about this insularity and aloofness so characteristic of these old Bostonian families.

Official History of the Canadian Medical Services 1939-1945. Vol. I: Organization and Campaigns. Edited by W. R. FEASBY, M.D. Ottawa: Canadian Ministry of National Defence, 1956. Pp. xii and 568. Illustrated. Price \$5.

IN modern times no Governments have shown a higher sense of responsibility for the care of sick and wounded in war than those of the English-speaking countries. This book gives a detailed account of the growth of the Canadian medical services from their minute permanent establishment of 166 all ranks in March 1939 and unfolds the story of their deployment. For the professional reader there is an abundance of technical detail; this, however, does not fog the issue for the layman who will appreciate the vast organization required behind the fighting man if he is to get the best of modern medicine and surgery wherever he needs it.

In the light of recent controversy it is interesting that the single medical corps for all three services before the war very rapidly divided into three separate ones, though the

Dental Corps remained common to all. The land campaigns receive the major attention and the arrangement of maps is outstandingly good. The Royal Canadian Navy has but one short chapter which hardly does justice to its tremendous expansion. The immensity of the British Commonwealth Air Training Plan with its striking rapidity of execution is stressed by the vast needs of its medical organization. To the whole book there is a backcloth of vigour and enthusiasm, characteristic of a young and proud nation, largely free from the fetters of tradition. If all its splendid forces are now dissipated they will at least be constantly remembered by the Pulheims system: a worthy, if rather prosaic, administrative medical legacy.

NEW EDITIONS

A Textbook of Psychiatry, by Sir David Henderson, M.D., F.R.C.P., F.R.C.P.ED., and the late R. D. Gillespie, with the assistance of Ivor R. C. Batchelor, M.B., F.R.C.P.ED., D.P.M., in its eighth edition (Oxford University Press, 35s.), has undergone careful revision, particularly in the discussion of etiological problems, and in the chapter on epilepsy. This book has always ranked as the most satisfactory comprehensive guide to psychiatry for the general physician, and in its new edition it maintains its right to this claim. Unlike so many textbooks on the subject, clichés, verbosity and the narrow outlook of the academic psychiatrist are all notable by their absence.

Shaw's Textbook of Gynaecology in its seventh edition (J. & A. Churchill Ltd., 32s. 6d.) has been revised by John Howkins, M.D., M.S., F.R.C.S., F.R.C.O.G. Although much of the original text has been preserved, Mr. Howkins has successfully brought the book up to date, thus effectively blending Shaw's outstanding powers of exposition with current advances. The main change is the addition of a chapter on tuberculosis of the genital tract. Other sections which have undergone careful revision include that on carcinoma of the cervix, and that on infertility. The illustrations, always an outstanding feature of this book, have also received careful attention, and there are 116 new ones in this edition. Bart's has every reason to continue to be proud of this product of its gynaecological department.

Clinical Laboratory Diagnosis, by Samuel A. Levinson, M.S., M.D., PH.D., and Robert P. MacFate, M.S., PH.D., in its fifth edition (Henry Kimpton, 93s. 6d.), is an excellent guide to the subject. It covers bacteriology, as well as biochemistry and hæmatology, and there are sections dealing with tropical diseases and forensic medicine. Each chapter is introduced by a short review of the relevant physiology and bio-

chemistry, so that the reader can understand the significance of the results obtained by various techniques described. It is too detailed for the medical student in this country, but an admirable reference book for him, as well for the clinician. For the trainee clinical pathologist or biochemist, it can be unreservedly recommended.

Orthopædic Nursing, by Mary Powell, S.N.M.C.S.P., Orthopædic Nursing Certificate, second edition (E. & S. Livingstone Ltd., 27s. 6d.). This excellent book describes and illustrates the essential bases of orthopædic surgery. The second edition brings up to date the principles and procedures described in the first. It is a little larger and more amply illustrated, but naturally enough, since basic principles have not changed in five years, the essential material in the book is the same as the earlier edition. It is a little disappointing that criticisms of the first edition appear to have been ignored: there is still no place in the index for anterior poliomyelitis; and although the book is much concerned with splints the precautions necessary for the safe use of the Thomas splint have not been amplified and are not adequate; the value of using suitable splints instead of plaster of Paris in the treatment of Colles' fracture is not mentioned. But the book as a whole is so good that it is invaluable to anyone interested in orthopædic surgery.

Surgeons All, by Harvey Graham, M.D., in its second edition (Rich & Cowan, 25s.) has had a chapter added, 'Postscript 1939-1956', which brings it up to date. It is a masterpiece of condensation, and an outstanding example of how medical history can be written in an attractive manner without any sacrifice of accuracy or perspective, and without the use of too many technical terms. In other words, this is a book which will appeal to the layman as well as to the doctor. It gives a superb picture of the development of surgery from ancient times, and as such should be compulsory reading for every medical student—having first been read, of course, by his teachers.

BINDING CASES

Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 5s. each post free. The cases are made to hold 6 copies of the advertisement pages have been removed; they are self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 13s. 6d. per volume; this includes the cost of binding case and return postage.

The contents of the March issue, which will contain a symposium on 'Gynaecology' will be found on pages at the end of the advertisement section.

Notes and Preparations see page 263.

Fifty Years Ago see page 267.

Motoring Notes see page A75.

Travel Notes see page A79.

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from 1st February, 1957***

ADVANTAGES

Superior therapeutic effect.
Little or no sodium and water retention

INDICATED ESPECIALLY

when cortisone has failed or when electrolyte
disturbance and water retention have occurred

DOSAGE: One quarter that of cortisone.

e.g. in adults: initially 20 to 40 mg. daily
maintenance 5 to 20 mg. daily

in children: initially $\frac{1}{2}$ to 1 mg./kg. daily
maintenance $\frac{1}{8}$ to $\frac{1}{4}$ mg./kg. daily

Transfer to DeCortisyl or PreCortisyl requires
no special precautions, other than maintaining
continuity of treatment in equivalent dosage.

Scored tablets of 5 mg.
Bottles of 30 and 100
Basic N.H.S. Price
(cost to chemist)
37/6 and 120/-



847 HARROW RD,
LONDON N.W.10

LS/21

New!

Adelphane

(0.1 mg. Serpasil + 10 mg. Nepresol)

FOR MILD AND MODERATE
HYPERTENSION
IN GENERAL PRACTICE

A combination of Serpasil (reserpine CIBA) and Nepresol (1,4-dihydrazinophthalazine sulphate) for those hypertensive patients not showing adequate response to Serpasil alone.

The components have a mutually potentiating action
and side effects are minimised.

Available in bottles of 25, 100 and 500

C I B A

'Adelphane', 'Nepresol' and 'Serpasil' are registered trade marks. Reg. user.

CIBA LABORATORIES LIMITED, HORSHAM, SUSSEX
Telephone: Horsham 4321 Telegrams: Cibalabs, Hprsham

1/7

NOTES AND PREPARATIONS

NEW PREPARATIONS

'ALBAMYCIN' tablets each contain 250 mg. of novobiocin, 'a new oral antibiotic effective in a wide variety of infections including many resistant to other antibiotics'. Novobiocin is said to give blood levels '10 to 50 times higher' than those attained with other antibiotics. Available in bottles of 16 and 100 sugar-coated tablets. (Upjohn of England Ltd., 4 Aldford Street, Park Lane, London, W.1.)

'AMENORONE FORTE' tablets each contain 50 mg. of ethisterone and 0.05 mg. of ethinylœstradiol and are intended for use in amenorrhœa of recent origin and as a pregnancy test. Available in boxes of 3 tablets. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'ASMACORT' tablets each contain prednisone, 1.5 mg.; ephedrine hydrochloride, 15 mg.; theophylline, 120 mg.; and phenobarbitone, 10 mg., and are intended for the treatment of asthma of 'moderate severity and between attacks'. Available in bottles of 20 and 100 tablets. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'CORTISPORIN' is a new antibiotic ointment, each gramme of which contains 5000 units of 'aerosporin' brand polymyxin B sulphate, 400 units of bacitracin, 5 mg. of neomycin sulphate, and 5 mg. of hydrocortisone (free alcohol), in a petrolatum base, and is intended for the treatment of bacterial infections and inflammation of the skin, the eye and the external ear. It is said to have an antibacterial range 'greater than that of any single antibiotic' and to be 'successful even against *Ps. pyocyanea* and *Proteus vulgaris*'. Skin sensitization and bacterial resistance are 'unlikely' and 'there is no likelihood of cross-sensitization or cross-resistance to other antibiotics'. Issued in tubes of 10 g., with special nozzle. (Burroughs Wellcome & Co., 183-193 Euston Road, London, N.W.1.)

'PECTAMOL' is a 'pleasantly flavoured' linctus containing 10 mg. of the citrate of the diethylaminoethoxyethyl ester of α : α -diethylphenylacetic acid. It is said to be 'particularly effective in suppressing dry, unproductive cough' as well as moderating 'productive cough of excessive intensity or frequency'. No side-effects have been reported following its use. Issued in bottles of 60 ml., 250 ml., and 2 litres. (The British Drug Houses Ltd., London, N.1.)

'SIGMAMYCIN' is a combination of tetracycline and oleandomycin. Its therapeutic range is similar to that of tetracycline, 'but the addition of oleandomycin gives enhanced activity against such gram-positive bacteria as staphylococci, pneumococci and streptococci'. Available in capsules of 250 mg., in bottles of 16 and 100. (Pfizer Ltd., 137-139 Sandgate Road, Folkestone, Kent.)

PHARMACEUTICAL NOTES

BOOTS PURE DRUG CO. LTD. announce that their prednisolone preparation, 'delta-stab', is now freely available in tablets of 1 mg. (in packs of 100) and 5 mg. Issued in bottles of 30, 100 and 500. (Station Street, Nottingham.)

PFIZER LTD. announce that their prednisolone preparation, 'deltacortril', is now freely available in tablets of 1 mg. (in packs of 100) and 5 mg. (in packs of 10, 20, 100, 500 and 1000). (137-139 Sandgate Road, Folkestone, Kent.)

FILM NEWS

La Presse Médicale announce that their 'annual prize for medico-surgical cinema', comprising 100,000 Fr. (which may be divided) and various other prizes, will be awarded during the last session of the course of 'Actualités médico-chirurgicales' to be held in Paris in March 1957. Any 16-mm. film which is not subsidized and not produced by a laboratory or firm may be submitted. The latest date for receipt of entries is February 28, 1957. Full details may be obtained from the Secrétariat, *La Presse Médicale*, 120 Boulevard Saint-Germain, Paris VI, France.

The Technique of Intramuscular Injection. This brief film strip, in colour, and the accompanying commentary describe the technique of giving an intramuscular injection. The pictures are clear, and excellent for teaching student nurses although the practice of injecting a standing patient is not to be commended. The commentary is less attractive, and sister tutors will probably prefer to speak spontaneously—and much more naturally. Copies of the film strip and commentary may be obtained free from Benger Laboratories Ltd., Holmes Chapel, Cheshire.

FORTHCOMING CONFERENCES

The Chronic Rheumatic Diseases will be the subject of a 'concentrated week-end course', with lectures, ward rounds and practical demonstra-

tions, to be held at the Rheumatism Unit of St. Stephen's Hospital, Fulham Road, Chelsea, London, S.W.10, on Saturday and Sunday, March 9 and 10, 1957. Full details may be obtained from the Secretary, Fellowship of Postgraduate Medicine, 60 Portland Place, London, W.1.

The Annual Conference of the National Association for Mental Health, the subject of which will be 'The Maladjusted Child', will be held at Church House, Westminster, London, S.W.1, on April 11 and 12, 1957. Full details may be obtained from The National Association for Mental Health, Maurice Craig House, 39 Queen Anne Street, London, W.1.

The *Harvey Tercentenary Congress* will be held at the Royal College of Surgeons in London, from June 3 to June 7, 1957, inclusive. The main theme will be 'A review of the present knowledge of the circulation'. The congress will be followed by a week-end conference, on the more personal and biographical aspects of William Harvey's life, at his birthplace, Folkestone, Kent, on Saturday, June 8, 1957. Further details and application forms for membership may be obtained from the Congress Secretary, 11 Chandos Street, Cavendish Square, London, W.1.

POSTING PATHOLOGICAL SPECIMENS

We have been asked to draw the attention of readers to the need for care when transmitting pathological specimens through the post. The Post Office allows such specimens to be sent by letter post provided they comply with rules which are laid down in a leaflet entitled 'Deleterious liquids or substances. Articles sent for medical examination or analysis', copies of which can be obtained from any post office. Occasionally, pathological specimens are sent through the post so badly packed or sealed that leakage occurs, constituting a real risk to the postal staff and contaminating other mail. It is pointed out that particular care is required in giving detailed instructions to patients who are given receptacles for specimens to be returned by them through the post.

GENERAL PRACTICE AND THE UNDERGRADUATE

A SURVEY published by the British Medical Students' Association shows that organized tuition in general practice is now provided in 22 of the 27 medical schools in the United Kingdom which offer facilities for clinical study. This shows a most commendable increase since 1953, when there were only 10 schools providing such teaching. The five schools in which there is no

organized general practice tuition are those of the Middlesex, St. George's, St. Thomas's, the West London Hospitals, and the Queen's University of Belfast. In those schools which provide tuition in general practice the scheme can be divided into four categories:—(a) 'Health centre' schemes operated by the University authority providing teaching for students. There are only two of these—in Edinburgh and Manchester. (b) 'Residential' schemes, in which the student spends some time living with the general practitioner. (c) 'Attachment' schemes, in which the student is attached to a general practitioner in the mornings for a given period of time, usually one to two weeks. (d) 'Day visit' schemes in which the student spends a day with a general practitioner.

CLEAN AIR ACT

THE New Year has seen the coming into force of certain of the provisions of the Clean Air Act, 1956. These include the provisions enabling local authorities to create smoke control areas in which the emission of smoke from buildings will be an offence. In such control areas, gas and other appliances in which smokeless fuel cannot be burnt satisfactorily will have to be altered or replaced. Other provisions which now come into force empower the Minister of Housing and Local Government to make regulations requiring furnaces to be fitted with smoke density meters, and all new furnaces, other than small domestic boilers, must be, so far as practicable, smokeless. The height of new chimneys other than those of houses, shops and offices will require approval by the local authority. Local authorities are now empowered to make by-laws requiring the provision in new buildings of such arrangements for heating and cooking as are calculated to prevent, as far as practicable, the emission of smoke.

RAIL TRANSPORT FOR PATIENTS

THE Department of Health for Scotland has issued a letter, reminding regional ambulance committees of the advantages of sending patients who have to travel long distances, by rail instead of by ambulance. Not only does this save petrol, it is often more comfortable for both sitting and stretcher patients. Arrangements between ambulance service and the railway authorities allow compartments to be reserved exclusively for patients and, if necessary, their escorts. Such patients are taken by ambulance to the station and are met at the other end by ambulance. Provided a patient comes 'within the category of an ambulance case', the entire arrangements for train-ambulance journeys becomes the responsibility of the ambulance service; it includes the cost of tickets for the patient.

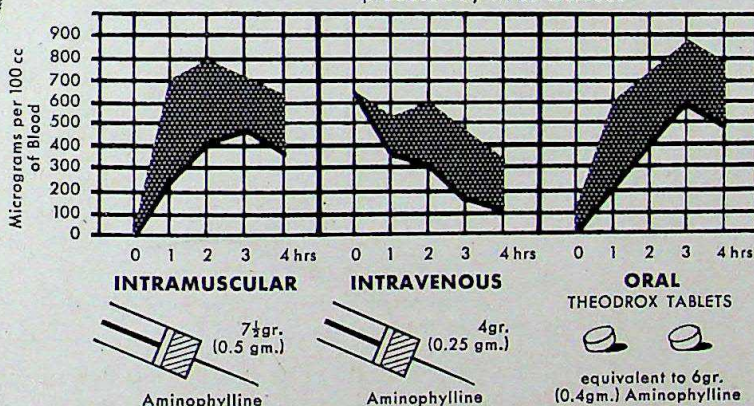
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**oral aminophylline therapy . . .
by producing High Blood Levels
without gastric distress**

BLOOD LEVELS OF AMINOPHYLLINE (expressed as theophylline)
— produced by three methods



The valuable properties of aminophylline can now be utilized to the full, simply and effectively—by the *oral* administration of 'Theodrox'. The serious disadvantage associated with the oral dosage of *plain* aminophylline—acute gastric distress—has been overcome. A high blood level of the active component, theophylline—such as could be obtained satisfactorily only by parenteral administration—is now possible. 'Theodrox' contains aminophylline combined with specially prepared aluminium hydroxide, and gastric discomfort is reduced to a minimum. When a degree of sedation is also required, tablets of 'Theodrox' With Phenobarbitone (containing gr. $\frac{1}{2}$ phenobarbitone) are indicated.

'Theodrox' tablets each contain gr. 3 aminophylline, and both forms of 'Theodrox' are available in bottles of 25, 100 and 1,000.

INDICATIONS

For the treatment of Bronchial or Cardiac Asthma; as a diuretic in Congestive Heart Failure; as a supplement to emergency treatment in Status Asthmaticus; Angina Pectoris.



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no dandruff**on this comb**

COMPLETE CONTROL of common dandruff in 92 to 95% of cases... control of seborrhoeic dermatitis of the scalp in 81 to 87% of cases... this represents the clinically proved effectiveness of SELSUN. It restores the scalp to a normal, healthy state, keeps it free of scales and excessive sebum for a period of one to four weeks after each application. Itching and burning usually stop after two or three applications. SELSUN is applied while washing the hair. It reaches all areas of the scalp, is simple and pleasant to use. Rinses out easily, leaving the scalp clean and odourless. Does not discolour the hair; leaves no greasy stains.

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Available in 2 and 4 fl. oz. bottles, with directions for use.

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FIGURES
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if necessary on medical grounds, for an escort. All the general practitioner needs to do is to inform the ambulance service that travel by train would be suitable.

FACTORY ACCIDENTS

IN 1955, the accident rate in factories was the lowest yet recorded, according to the annual report of the Chief Inspector of Factories: the accident index was 89.2 (1950 being taken as 100). The number of accidents increased to 188,403, compared with 185,167 in 1954—an increase of 1.2%, but the factory population increased by 2.5%. The number of deaths was 703, compared with 828 in 1951. The accident rate was about 26 per 1000 for men, and about 10 per 1000 for women. There were 583 (20 fatal) cases of industrial poisoning and diseases, compared with 483 (15 fatal) in 1954. Chrome ulceration accounted for the highest number of cases (261), followed by epitheliomatous ulceration (211, with 18 deaths). There were 69 cases of lead poisoning, and for the sixth successive year there were no fatal cases. There were no deaths among the 15 cases of anthrax.

TREATMENT OF RABIES

THE third WHO expert committee on rabies, at a recent meeting, confirmed the 'striking effectiveness' of serum plus vaccine in the prevention of persons severely bitten by a rabid animal. It was stressed that it is necessary to give a complete course of vaccine along with the serum therapy. Because of the danger of side-reactions, it is recommended that serum be given only in very severe exposures after testing the patient for sensitivity. A new technique for protecting persons whose occupation exposes them to the risk of bites by rabid animals was described. This consists of providing basic protection by giving very small doses of chicken embryo vaccine, or a few doses of ordinary nerve tissue vaccine, followed by a single booster dose of vaccine after being bitten, instead of the long (14 to 21 days) schedule of inoculations now performed. For the immediate treatment of wounds inflicted by animals suspected of having rabies, immediate cleansing with soap and water is recommended, followed by cauterizing with nitric acid on parts of the body where this can be used without danger. This, in turn, is followed by the injection of serum around the site of the bite.

BOVINE TUBERCULOSIS

FIGURES just issued by the Ministry of Agriculture, Fisheries and Food show that there are now 6½ million attested cattle in Great Britain, representing 67% of the total, compared with

60% a year ago. Wales has the best record, with 85% of its cattle attested, followed closely by Scotland with 84%. The figure for England is only 60%.

LUMINOUS CLOTHING

A NEW type of 'reflective yarn' has been developed for outdoor clothing which glows a bright silver under car headlights, according to a note in the *Connecticut State Medical Journal* (1956, 20, 901). Garments made of this grey thread look like any other except when viewed from a car at night. Tests are said to have shown that a driver travelling at 30 miles per hour could see a child in 'an ordinary snowsuit' 100 feet away with low-beam headlights, giving him only 2.2 seconds' available stopping time. The same garment made with reflective yarn was visible 525 feet away, allowing nearly 12 seconds' margin. The implications from the point of view of road safety at night are obvious.

LONG-TERM PRESCRIBING

THE following prescription was received by a pharmacist on Christmas Eve, according to *The Chemist and Druggist*:—

'Tab. alumin. hydrox.

Mitte 150

Sig.: One every two or three years'.

PUBLICATIONS

Clinical Examinations in Neurology, by Members of the Sections of Neurology and Physiology of the Mayo Clinic, covers ground already familiar from similar productions, of which Monrad-Krohn's handbook is probably the most widely used in Britain. As might be expected from its source, it is more frankly physiological in its approach and it also deals clearly and authoritatively with such ancillary methods of investigation as electroencephalography and electromyography. Full of reliable information and advice, it can be strongly recommended to any physician who is called on to carry out neurological examinations. The quality of printing and binding is beyond reproach, and renders the book a pleasure to handle. (W. B. Saunders Co., price 52s. 6d.)

Refresher Course for General Practitioners.—Volume 3 of this series consists of a series of specially commissioned articles published in the *British Medical Journal* between April 1952 and September 1953, and fully revised for publication in book form. It contains 60 articles covering a wide variety of subjects, ranging from 'Psychiatric treatment and the law' to 'Recurrent boils'. (British Medical Association, price 25s.)

The Complete Cookery Book for Diabetics, by Iris Holland Rogers, of the British Diabetic Association, can be wholly recommended to all diabetics as a reliable and practical guide to the enjoyment of good food. (H. K. Lewis, price 6s.)

Expert Committee on Insecticides, Sixth Report, WHO Technical Report Series No. 110, deals with the whole subject of insecticide equipment: specifications, methods of use, and maintenance. (H.M. Stationery Office, price 3s. 6d.)

Junior Health and Hygiene Manual, by the Medical Officer for St. Pancras, and his deputy, is a wholly successful attempt to provide instruction in healthy living and hygiene for young people. School teachers and club leaders will find it particularly useful, and it will prove most useful to practitioners who are asked to lecture to young peoples' clubs or the senior forms in schools. (The British Red Cross Society, price 2s. 6d.)

Directory of Contributory Schemes for the Year 1956 is published by the British Hospitals Contributory Schemes Association (1948), Royal London Buildings, Baldwin Street, Bristol, 1. Price 10s. post free.

OFFICIAL NOTICES

Prednisone and Prednisolone.—The Ministry of Health, in conjunction with the Department of Health for Scotland and the Ministry of Health and Local Government, Northern Ireland, has made arrangements with U.K. manufacturers for prednisone and prednisolone which will enable preparations of these substances to be supplied on prescription from February 1, 1957.

Remuneration of Chemists.—The Minister of Health has approved the following alterations in the terms of service for chemists:—(a) An additional 1½d. per prescription to be paid on all prescriptions, other than those for trusses and hosiery, dispensed during the calendar year 1955. (b) An additional 2½d. per prescription to be paid on all prescriptions other than those for trusses and hosiery, dispensed from January 1, 1956.

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the year ended 31st December, 1955. Part II. On the State of the Public Health.—In this, his annual report for 1955, the chief medical officer of the Ministry of Health notes that for the second year in succession no case of smallpox was recorded. On the other hand, the acceptance rate for primary vaccination of infants is still disappointingly low—varying between 5.1% and 70.1% in different areas. The stillbirth rate—at 23.3 per 1000 total live and still births—has

remained relatively stable since 1948, and the view is expressed that 'it is disturbing to find that for seven years there has been no progress in this field that has had any effect on national rates'. Disappointment is expressed at the steady decline in breast feeding, particularly in teaching hospitals. In these the rate was only 67.67% compared with 76.06% for all infants in institutions, and 82.4% for infants born at home.

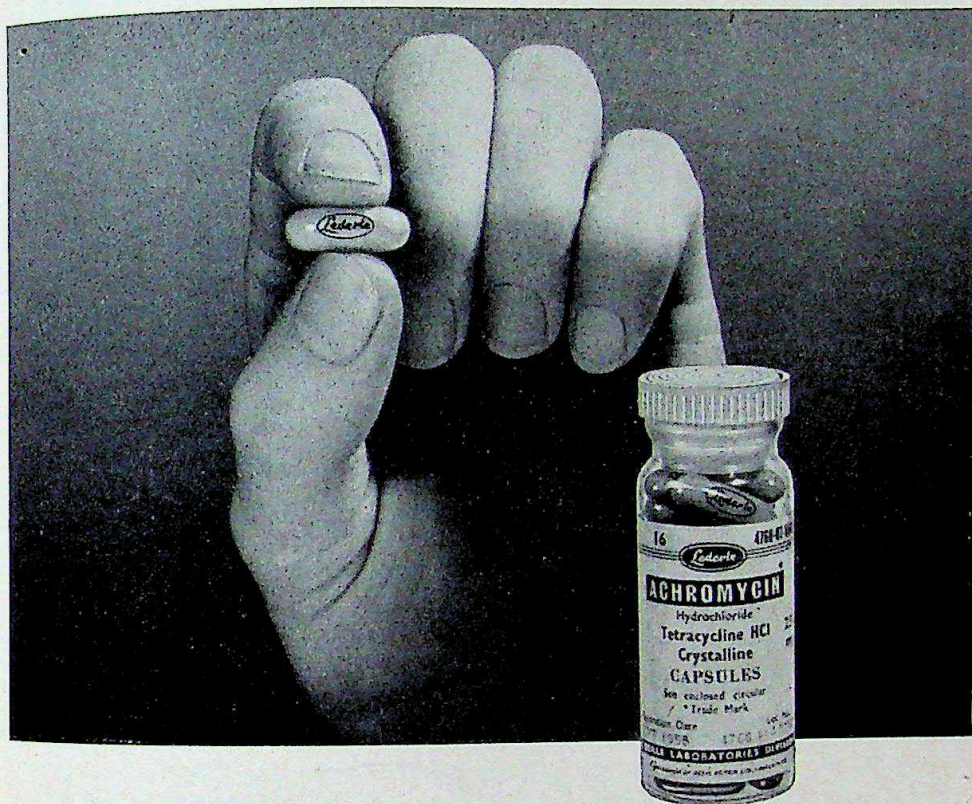
There was an increase of 1,245 deaths from cancer: 847 men and 398 women. Carcinoma of the lung accounted for 826 more deaths in men—an increase of 5.9% over the 1954 figure—and for 30.77% of all male cancer deaths. Similar figures for females are 115 more deaths—an increase of 4.9% and representing 5.68% of all female cancer deaths. The view is expressed that 'the practice of those countries abroad which do not countenance smoking in theatre cinemas or even in public transport is one that deserves at least study, if not imitation'. In both sexes the mortality from leukaemia is now more than twice the figure recorded in 1936. For the first time since 1947 the number of new patients with syphilis attending venereal disease clinics with infections of less than one year failed to fall. The clinic incidence of gonorrhoea in both sexes increased, and 'it is now clear that there has been no appreciable improvement in the control of this disease during the last five years'. (H.M. Stationery Office, price 9s.)

The Health of The School Child.—In this, his report for 1954 and 1955, the chief medical officer of the Ministry of Education states that 'the health of the great majority of the children was good'. Only 1.46% of them were considered to be in poor physical condition in 1955, compared with 2.55% in 1952. Child mortality continued to decline. In 1955, 2,755 children aged 5-14 years, died, compared with 9,047 in 1938. Over this period deaths from tuberculosis fell from 973 to 54, and deaths from diphtheria from 1,733 to five. On the other hand, twice as many children in this age-group now die annually from violence as die from all the infectious and respiratory diseases put together. Although body-lice- and flea-infested children are now rarely found, there are still a quarter of a million children with verminous heads. (H.M. Stationery Office, price 6s.)

CORRIGENDA.—In our January issue (p. 7) 'ilotyacin' was given as one of the proprietary names for tetracycline. This, of course, is not the case. 'Ilotycin' is the proprietary name of Eli Lilly & Co. Ltd. for erythromycin. The proprietary names for tetracycline are 'achromycin' (Lederle) and 'tetracycl' (Pfizer).

In table 1 on p. 66 of our January issue, 'ancolan' was given as a proprietary name for phenindamine, whereas it is 'The British Drug Houses' proprietary name for meclozine.

On p. 31 of our January issue it was incorrectly stated that allylisopropylacetylurea contains bromine.



dispelling the element of doubt

TODAY—with so many antibiotics available—it is always sound practice to specify ACHROMYCIN *by name* whenever true broad-spectrum activity is desired. In this way you are completely assured that the patient receives precisely the treatment you intend. Offered now in no less than fourteen presentations, ACHROMYCIN tetracycline is particularly widely used in capsule form. On every capsule appears the name Lederle—your finest assurance of consistent antibiotic potency and unfailing dependability.

Capsules of 50 mg. — in vials of 25 and 100. Capsules of 250 mg. — in vials of 16 and bottles of 100 and 1000

ACHROMYCIN^{*}

TETRACYCLINE

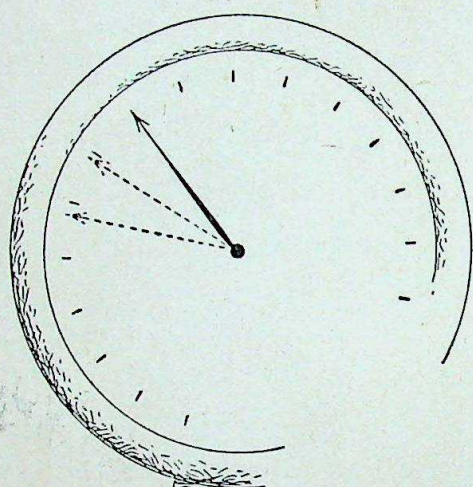
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Also available in the following forms: Ear Solution • Intramuscular • Intravenous • Ointment 3%
Ointment (Ophthalmic) 1% • Ophthalmic Powder Sterilized • Oral Suspension • Liquid Pediatric Drops
SPERSOIDS^{*} Dispersible Powder • Soluble Tablets • Syrup • Tablets • Troches



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Cyanamid OF GREAT BRITAIN LTD., London, W.C.2



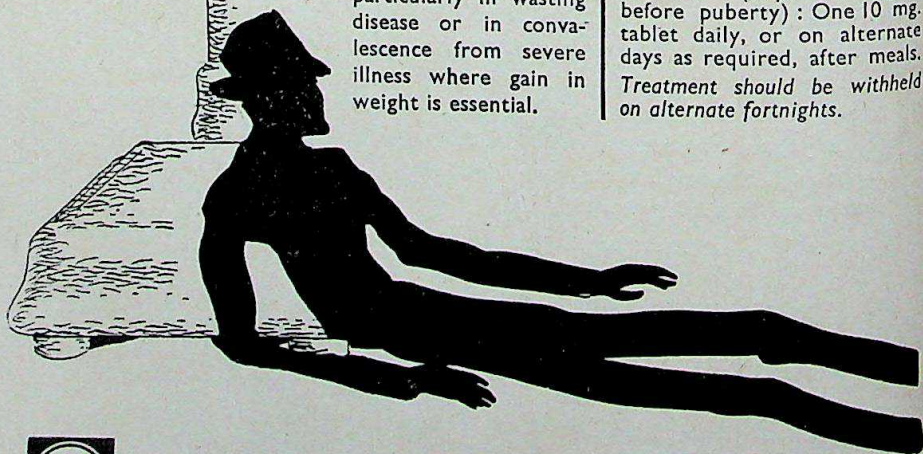
For
essential
weight
gain . . .

STENEDIOL^{*}

*The most potent non-virilising
tissue building Steroid*

*Free from the side-effect of virilisation in the recommended dosage, STENEDIOL is indicated particularly in wasting disease or in convalescence from severe illness where gain in weight is essential.

Dose : Adults (both sexes) : One 10 mg. tablet thrice daily after meals : higher doses up to 150 mg. daily may be given. Children (boys and girls before puberty) : One 10 mg. tablet daily, or on alternate days as required, after meals. Treatment should be withheld on alternate fortnights.



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THE PRACTITIONER

Fifty Years Ago

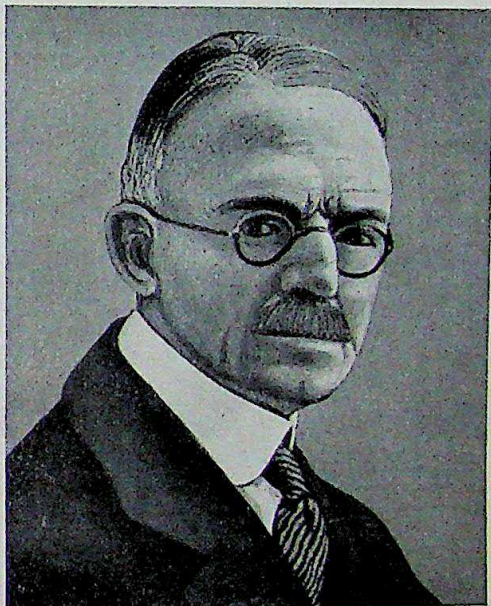
There is one great difficulty in modern times: the choosing not only what to know but what to trust; what not to know and what to forget'.—John Brown: *Horæ Subsecivæ*.

FEBRUARY 1907

THE "cancer curer" we have always had with us; we are now suffering from a severe visitation of the "cancer crank". By this 'Notes by the Way' mean 'the highly scientific person who, knowing nothing of practical medicine, and indeed often holding it in the contempt naturally born of ignorance, attacks the problem of cancer from a purely biological standpoint, and having satisfied himself that it is all a case of the anomalous behaviour of certain cells, forthwith publishes this as an epoch-making discovery. He then finds something which he persuades himself will eliminate the peccant cell and reduce the anarchy of disease to the order of health . . . The possession of a medical degree, though it may to a certain extent be a test of knowledge, does not necessarily confer wisdom. Men whose academic honours almost exhaust the alphabet are often utterly lacking in judgment and critical power. They allow themselves to be carried away by the wind of every new doctrine, and do infinite harm by premature reports of the virtues of the latest therapeutic novelty. These men are especially apt to be led astray by the cancer crank . . . By all means let cancer be fully tried, but to vaunt it as a cure', before anything at all like a cure has been achieved, is a crime against mankind . . . A discovery either of the germ or of the remedy can only be hindered by the premature claims of frothy enthusiasts'.

The fishy theory of leprosy', advocated 'with ability and persistence by Mr. Jonathan Hutchinson in *The Times* and elsewhere, was of course originated by that distinguished physician. It is the oldest theory of all, and had required an ancient and fishlike smell that made it sink in the nostrils of the profession till he thickened it into an artificial freshness'. That 'undue' noise was already a problem years ago is evident from a comment 'The Nuisance': 'There is, we believe, a society in London which professes to make the abatement of this evil the object of its existence, but have not observed that its labours have been crowned with any appreciable success. A Society for the Suppression of Unnecessary Noise' has recently been founded in New York. This shows that people are becoming restive under an infliction which is becoming more and more a nuisance and a danger'. Under the heading 'Place aux Dames' the author writes: 'One by one the strongholds of

medicine have fallen to the conquering blast of the feminine trumpet. Women can now get medical degrees at all Universities except Oxford and Cambridge, over which there still hangs the shadow of an impenetrable conservatism; and they are admitted by all corpora-



Sir Raymond Henry Payne Crawford, M.D.,
F.R.C.P. (1865-1938)

tions except the London College of Physicians and the English College of Surgeons. The ladies, however, have not fought so strenuous a fight against the forces of prejudice without learning how to carry the warfare to a victorious issue. They are now summoning the fortress of surgery in Lincoln's Inn Fields to surrender. They urge that since they last battered at its doors in 1895, the entry of women into the medical profession has steadily increased, and the total number now on the *Medical Register* is over 750 . . . We think the ladies have made out a good case for themselves, but we cannot feel much confidence that they will succeed in forcing their way into the sacred precincts of the College of Surgeons'.

The opening article in this number, 'The Treatment of Some of the Forms of Gout', is by Arthur P. Luff, M.D., F.R.C.P., Physician to St. Mary's Hospital. Arthur Pearson Luff,

the centenary of whose birth occurred last November, became lecturer on medical jurisprudence and toxicology at St. Mary's in 1887, assistant physician in 1890, and full physician in 1896. A recognized authority on gout, he enjoyed a lucrative practice, for he was not afraid to treat acute attacks of the disease with morphine, but it is interesting to note that in this paper he states: 'The administration of opium or morphine should, if possible, be avoided owing to the risk of its deficient elimination, and also on account of its diminishing the amount of urine, and its tendency to derange digestion and to check hepatic metabolism'. Archibald Young, M.B., C.M., Dispensary Surgeon, Western Infirmary, Glasgow, describes 'Posterior Tarsal Resection of the Foot by the Method of Mikulicz and Wladimiroff'.

Raymond Crawford, M.D., F.R.C.P., Physician to King's College Hospital, discussing 'Tricuspid Stenosis', reports seven cases in which its existence was not suspected. Scholar-physician and administrator, Sir Raymond Henry Payne Crawford was born in 1865, was educated at Winchester, Oxford, and King's College, London, and graduated B.M., B.Ch. in 1894. He was elected assistant physician at King's College Hospital in 1898, physician in 1905, consulting physician in 1930, and was knighted in 1933. At the Royal College of Physicians he served as registrar for thirteen

years, and he helped to found the Section of the History of Medicine of the Royal Society of Medicine. He died in 1938.

Thomas Lewis, D.Sc., M.B., B.S., Fellow University College, London, deals with 'The Interpretation of Sphygmograph Tracings, and of Tracings Produced by Compressing the Brachial Artery'. The title of the Prize Essay by G. H. Bate, L.S.A., of Bethnal Green is 'The Relative Value and the Selection of Diuretics'. The 'hero' of the 'Famous Quack' series this month is Joshua Ward ('Spot Ward

Among the books reviewed are Sir Patrick Manson's 'Lectures on Tropical Diseases', R. Tanner Hewlett's 'Pathology, General and Special, for Students of Medicine'; Osler's 'Æquanimitas' ('couched in terms clear, illuminating, and not infrequently rising to a very high degree of eloquence'); and Alfred T. Schofield's 'Unconscious Therapeutics, or the Personality of the Physician'.

'During the present month Mr. H. K. Lewis will establish his circulating library in more convenient quarters adjoining the old premises at 136, Gower Street'.

According to 'Practical Notes', 'If the rash of measles does not come out well, warm drinks and a hot bath will often hasten its development'.

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THE PRACTITIONER

No. 1065

MARCH 1957

Volume 178

THE MONTH

Now that the populace, rightly or wrongly, is becoming so 'cancer-conscious', it is inevitable that our symposium on 'Gynæcology' this month

should be introduced by two articles on carcinoma of the uterus. We would particularly commend to readers Mr. **Symposium** Kenneth Bowes' thoughtful article on treatment. Too often, as he points out, 'when statistics are employed in analysis "things are not always as they seem"'. Statistics divorced as they so often are today from clinical judgment can so easily prove confusing, if not actually misleading. Mr. Bowes indicates the crux of the problem when he says that 'further work, based upon more accurate details of the stage, site, and type of growth will have to be available for the proper answer to be given to this question'—i.e. the correct form of treatment. The last few years have witnessed a tremendous advance in the cytological diagnosis of carcinoma of the uterus, and this important diagnostic development is ably summarized by Dr. Bamforth. The other articles in the symposium deal with aspects of gynæcology which are all within the ken of the family doctor—whether it be the indications for, and results of, hysterectomy, the diagnosis of ovarian tumours, or the conditions which he is called upon to treat himself, such as leucorrhœa and the gynæcological problems of adolescence. The symposium concludes with a review of a problem which is assuming ever-increasing importance—'the female contribution to the sterile marriage'.

Curative and Preventive Medicine THE present artificial separation of preventive and curative medicine is largely the result of the original unfortunate confusion of thought which looked upon 'public health' and 'preventive medicine' as synonymous and equivalent terms. The separation has been accentuated by the current craze for specialization. 'Public health' is undoubtedly 'preventive medicine', but so also is good general practice. If this were fully appreciated, much of the present controversy concerning the relative functions of local authority medical officers and general practitioners would disappear. Fortunately, the more thoughtful among both medical officers of health and general practitioners appreciate the essential unity of their respective spheres of work. This unitarian concept was admirably epitomized by Dr. C. Metcalfe Brown, the medical officer of health for Manchester, in our recent sym-

posium on 'Home Care and Nursing' (*The Practitioner*, 1956, 177, 48): 'The general practitioner is the doctor to the family and as such has the first and the last say in the care and treatment of each member of the family. The preventive service and the hospital service are there to help the family doctor, not to displace him'.

In practice, however, we are faced with the illogical tripartite organization of the National Health Service, which works to the benefit of no-one except the pigeon-holing bureaucrats in Savile Row. It may well be that our national gift for making the unworkable work may overcome this obstacle. There are undoubtedly signs, in certain areas at least, that reasonably minded medical officers of health and general practitioners are evolving a method of cooperation based upon mutual understanding of each others' difficulties and a common desire to give the ratepayers in these areas the best possible medical care. Whether a gradual development of such schemes will overcome the administrative difficulties inherent in the present organization of the National Health Service is doubtful, and sooner or later the time will come when administrative, if not Parliamentary, action will be required. In a recent issue of *The Medical Officer* (1957, 97, 31), Dr. Gerald Ramage, the county medical officer of health, Staffordshire, propounds a scheme which is deserving of the most careful consideration by both general practitioners and medical officers of health. Unfortunately, he seems to assume that 'curative' and 'preventive' medicine are two entirely separate subjects but his detailed scheme for general practitioners taking over many of the duties at present covered by local authority medical officers provides a useful if provocative, basis for discussion. Has the time not come when two or three representative medical officers of health and an equal number of experienced general practitioners should get together informally and thrash out a scheme which will form the basis for long overdue reforms in the National Health Service, so far as it concerns the work of local authorities and general practitioners?

Of the many contributions which the general practitioner can make to the health of the nation, not the least important is by providing an accurate picture of the incidence of disease. As the traditionally 'killing' diseases come under control, mortality rates

Illness in become increasingly less reliable as a guide to national health. For this purpose their place must now be taken by morbidity rates, and for these we are to a large extent dependent upon the general practitioner. This is admirably brought out by a survey carried out by thirteen practitioners in Wigtownshire, and reported in the *Health Bulletin* (1956, 14, 69) issued by the Department of Health for Scotland. The population covered by these practitioners is approximately 19,000, of whom some 1,700 are children of pre-school age. During the course of one year these practitioners made an inventory of the reasons for calls on their

professional time in respect of children of pre-school age.

Their report shows that during the year 944 such children were attended, and 1,380 individual illnesses or accidents were recorded. This involved 1,989 visits and 902 consultations: i.e., 1.46 illnesses per sick child, and 1.44 visits and 0.65 consultation per individual illness. Of the detailed figures provided, perhaps the most interesting are that infections of the upper respiratory tract were the most frequent cause of illness, being responsible for 19 per cent. of illnesses, that the second numerically most important illnesses were those to which only a symptomatic diagnosis could be given (11.6 per cent.), and that there were only eight instances of deficiency states, including four of anæmia, two of malnutrition and one of rickets. That such a survey gives a more reliable picture of the true incidence of ill health is interestingly illustrated by the fact that in the whole of Wigtownshire, which has a population of around 32,000, in 1953 there were only four deaths among children aged 1 to 4 years: one each attributed to measles, malignant tumour, congenital malformation, and violence.

As the British Parliament learned to its cost in the pre-1914 era, no-one is more adept than an Irishman at befogging the issue with words. On the other hand, he can be equally adept at going straight to the

Anatomy: root of a problem and picking out the essentials from a U and Non-U morass of pedantic irrelevancies. Professor M. A. MacConaill, professor of anatomy in University College, Cork, comes into the second category. In a brilliant essay in a recent issue of the *Irish Journal of Medical Science* (January 1957, p. 15) he discusses the differences between University (U) and non-university (non-U) anatomy. His thesis is a simple one. A university is a place of scholarship, and true scholarship can be had in anatomy. 'Such scholarship should be demanded from the undergraduate in medicine just as we demand it from the undergraduate in arts'. He 'asserts boldly that the reputed fruits of an education in arts can be obtained just as surely by a thorough training for the second university examination in medicine. A man who has learned to use his hands and his eyes in good dissection is in truth the mirror-image of a sculptor . . . The man who has learned to write clearly, concisely and consistently upon anatomical facts and principles has shown a mastery of grammar, logic and rhetoric sufficient to satisfy even an Abelard or an Aquinas'.

In his opinion the Bible of anatomy is the human body—a phrase coined in an age when 'the Bible was the classic of the common man and it helped to breed a sharp concision and a stark directness that are disappearing as the Bible is less and less read'. This has been followed by a corresponding decline in what he calls 'a classical temper of thought in medical education'. "Quain's Anatomy", the anatomist's English classic has gone, whilst 'the most recently issued textbook is alarming in its sloppiness, bad editing and

grossly insufficient content'. Professor MacConaill's provocatively brilliant exegesis should be read and pondered by all concerned with the future of the profession. The crux of the problem will be found in his peroration. Unless the anatomist can indeed make the dry bones live, anatomy can never take its place as the modern equivalent of a sound training in the classics.

THE total expenditure on nurses' uniforms in the hospital service must approach £1 million each year, and laundering probably costs another million, according to a contributor to the *Nursing Times* (1957

National Uniform for Nurses 53, 47). A suitable national uniform for nurses, it is suggested, would not only lead to considerable savings, but would also save a great deal of unnecessary work and irritation for hospital staff generally. At the present time a nurse's uniform remains the property of the hospital supplying it. This means that a sister or nurse has to return her uniform when leaving a hospital and be supplied with a new one at the hospital to which she is moving. Apart from the practical advantages that would accrue from the introduction of a national uniform, the view is expressed that 'the majority of nurses would welcome a uniform designed in accordance with present-day needs and with an eye to æsthetic as well as aseptic considerations'.

This suggestion received sympathetic editorial consideration (*Ibid.*, p. 59), although it is admitted that 'any subject as emotionally charged as what nurses should wear is bound to produce heated arguments and a conflict of intensely personal views'. The one definite recommendation made is that the apron should be 'banished to its proper place'. 'It should be kept in the ward and donned for its protective purpose only—not worn as uniform or to hide an ungainly dress beneath'. Dress designing, it is said, 'is an art in which nurses are not skilled', and it is suggested that the colour of the uniform should be left to the authorities who advise on the modern use of colour in ward decoration. Should a national uniform be decided upon, certain criteria are laid down with which it should comply. It should fit the wearer—'not having to be gathered into some sort of shape by a clumsy belt'. It should be related to the style of today—'not of a century ago with gathers and tucks'. Tradition clings to the nurse's cap, 'which is a badge of distinction—no less and no more! But a cap need be neither a coif nor a veil, nor a butterfly attachment apparently about to take flight'. The *Nursing Times* obviously finds it difficult to decide whether the cap should stay but feels that there is much to be said for the suggestion that it might be retained as 'the distinctive badge of the nurse the world over'. No mere male is going to be rash enough to become involved in such delicate problems, except to the extent of expressing the view that there are certainly some nurses' uniforms which could be improved both practically and æsthetically.

THE TREATMENT OF CARCINOMA IN THE CERVIX AND BODY OF THE UTERUS

BY KENNETH BOWES, M.D., M.S., F.R.C.S., F.R.C.O.G.

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UNTIL the end of the 1939-45 War, treatment of carcinoma in the uterus, whether situated in the body or cervix, was provided by the alternative methods of operation or irradiation. In general, irradiation was advocated for cervical cases and operation for malignancy in the uterine body. There were, of course, workers whose methods were exceptions to this general policy. Bonney, for example, always advocated the Wertheim hysterectomy for carcinoma of the cervix when possible, and the staff of the Radium-hemmet in Stockholm in general used radium for the treatment of corporal cancer.

THE PRESENT POSITION

Although in our present state of ignorance as to the mode of origin and the spread of cancer, surgery and irradiation still provide our measures of therapy, changes have taken place in outlook since the end of the War. No longer is it a question of 'either' operation 'or' irradiation, for their relative merits and disadvantages when used separately are more or less equal, and the improvements in surgical approach gained by modern anæsthesia, blood transfusion, the antibiotics in preventing infection, and the more effective training of gynæcological surgeons, have been counter-balanced by the advances made during the same period by radiotherapists. Here it may be stated that the position as regards treatment of uterine cancer has been one of progress and results continue to improve.

The changes in outlook which have taken place and merit an article such as this at the present time are fourfold. In the first place, operation and irradiation are not mutually exclusive methods. As Meigs (1956) remarks, 'we are now trying to substitute intelligence for dogmatism in the treatment of carcinoma of the cervix, both radiation and surgical'. Secondly, if the methods are not exclusive, then either may be tried to redeem the failures of the other. Thirdly, in an attempt to improve results both methods may be employed sequentially: for example, many workers now use preoperative radium treatment to kill off the growth before removing it. Finally, attempts are being made by histological and cytochemical changes in irradiated tissues to determine whether or not the response of a tumour to irradiation is favourable. These factors lead to the main trend at the present time: the individualization of treatment to the particular patient and her tumour. Thus the practitioner may find that patients with uterine carcinoma whom

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he refers for treatment may be treated in several different ways although they perhaps seem to have much the same type of lesion on ordinary clinical examination. This may be confusing, and it is with the idea of showing the reasons behind the therapy that this article is concerned in an attempt to clarify the issue as it is seen at the present time.

Another change which has occurred since 1945 is in relation to the very early deviations from the normal which may occur in tissues and which may or may not progress to clinical invasive cancer. Before 1945, the question of pre-cancerous lesions, or lesions such as we now describe as carcinoma *in situ*, was only being discussed at a few centres, and diagnosable cancer was taken to be clinically evident disease with biopsy proof of invasion.

PATHOLOGICAL CONSIDERATIONS

Until some new approach in research reveals a better method of treatment, we have to base our use of surgery and irradiation on pathology. The end-result in cancer seems to depend ultimately upon the relationship between the type of growth and the resistance it encounters in the host's tissues, rather than upon the time and type of treatment. Probably the cancer starts as an alteration in the biological activity of a small area of cells or perhaps several such areas. The cells multiply and overcome the resistance of surrounding tissues. Satisfactory treatment needs effective local treatment either by surgery or irradiation, and also extensive treatment of the lymphatic field by the same agents. Carcinoma in the uterus embodies two quite different forms of cancer. That of the endometrium corresponds very much to intestinal cancer. Both are glandular carcinomas of relatively favourable malignancy (to use an Irishism); the prognosis of both is adversely affected by penetration into the underlying muscle tissue; and lymphatic gland involvement is later in the course of the disease and definite groups of glands are affected. Cancer of the cervix on the other hand bears some comparison to cancer of the breast. The primary growth is more malignant than that of the uterine body; spread occurs early in a rich field of lymphatics which drain to several groups of glands. Just as the general surgeons are now trying to individualize the treatment of their cases of cancer of the breast because they have realized the disadvantages of radical mastectomy, similarly the gynaecological surgeons have to weigh the pros and cons of the Wertheim operation.

THE VERY EARLY STAGES OF CARCINOMA

The desire to obtain earlier evidence, either of the existence of malignant disease, or of its possible precursors, so that treatment can be applied more effectively or even prophylactically, has led to much discussion in relation to uterine neoplasms, although the same ideas have been applied to other structures. In the case of the cervix there is no doubt that cellular changes as contrasted with typical invasion of deeper tissues can occur and be followed by true clinical carcinoma. These cellular changes of nuclear abnormality and hyperplasia are given a series of not very satisfactory

terms: carcinoma *in situ*, intraepithelial carcinoma, and pre-invasive carcinoma. They may be found associated with any type of cervical appearance on ordinary examination and nowadays may be diagnosed when the vaginal smear is used. The diagnosis of intraepithelial carcinoma is a momentous one which can only be made by a very expert pathologist with considerable experience in gynaecological pathology. Moreover, the diagnosis entails not merely evidence provided by the smear, but also by biopsy, and this means the examination of a ring of tissue round the external os. The question also arises as to whether the pathologist can differentiate between the tissue being really pre-invasive or in an early stage of invasion.

Thus the first disturbing question for the clinician is: How accurate can this diagnosis be? In seeking the answer he has of necessity to rely on the judgment of his pathologist although he should be able to ask specific questions. The clinician's responsibility, however, does not end with the diagnosis. His next question is: Does clinical invasive carcinoma supervene upon this *in situ* growth? In other words, is *in situ* growth a true cancer? The answer seems to be that it can become a true cancer, but not invariably. Carcinoma *in situ* seems to occur in a younger age-group than does clinical cancer (8 to 10 years younger) as would be expected. Series of cases have now been reported in which clinical cancer supervened at a variable interval of 1 to 17 years. Noteworthy evidence of this is provided by Kottmeier (1956) who followed 26 untreated cases, 42 per cent. of which became invasive cancer within 1 to 19 years. Petersen (1955, 1956) followed 127 cases similarly; 4 per cent. of these became truly malignant in one year, 11 per cent. in three years, and during nine years 34 out of the total of 127. The third question of the clinician is: If *in situ* carcinoma is an identifiable condition, and if it is followed by a definite percentage of true invasive cancer, what treatment is merited? This will be discussed later.

In the case of cancer of the uterine body the same question arises as to whether states precursory to true clinical cancer occur. Many clinicians have been struck by the frequent association of obesity, a late menopause, a small number of children and of diabetes mellitus, with carcinoma of the uterine body. From such findings a pituitary endocrine factor has been suggested. Preceding hyperplasia of the endometrium has also been implicated by some authorities (Rigo, Scipades and Vaczy, 1950) and some have even gone so far as to suggest that an atypical form of hyperplasia may represent a carcinoma *in situ* here (Hertig and Somers, 1949). Others (McBride, 1954) have failed to trace any connexion between the two conditions.

LYMPHATIC SPREAD AND GLAND INVOLVEMENT

The cervix, with its function as a barrier to infection of the upper genital tract, has an extensive lymphatic field. The upper part of the uterine body has a much less extensive one. Thus, gland involvement is much more common and occurs at an earlier stage in cervical than in uterine body cancer. Even in stage I cases of carcinoma of the cervix such involvement is

found in about 18 to 20 per cent. of cases. Gland involvement in corpus cases has been searched for less diligently, but seems to be present in a smaller number, particularly if the lower part of the cavity is not affected by the growth. This possibility of gland enlargement, even in early cases of cancer, has always been a strong argument in favour of surgical treatment where possible. There is evidence, however (Morton, 1947; Brown *et al.*, 1951; Kottmeier, 1953; Cherry *et al.*, 1953), that irradiation may favourably affect carcinoma in the glands either directly or indirectly if the response of the primary tumour is a good one.

THE REACTION OF THE TUMOUR TO IRRADIATION

Irradiation in favourable cases produces death in the tumour cells and also changes in the surrounding cells of the normal tissues. In carcinoma of the cervix attempts have been made to assess the sensitivity of the growth to irradiation, with the idea of helping to reach a decision as to whether this should be continued as the treatment or whether operation should be done. Repeated biopsies have been made (Glucksmann and Spear, 1945), vaginal cytological changes have been studied by smears (Graham, 1947; Graham and Graham, 1955; Gusberg, 1956), and clinical assessment by observing the shrinkage of the growth has been noted. The evidence is still conflicting, but the methods may help in selection of cases for treatment. Besides studying the effect of irradiation on the tumour cells, the Grahams consider the response of the cells of the normal tissues to be more important in assessing response.

TREATMENT OF CARCINOMA OF THE CERVIX

This may be more easily discussed according to the stage of the disease present in the patient. For this purpose the most satisfactory classification is: (i) Intraepithelial carcinoma. (ii) Clinically invasive carcinoma. (iii) The advanced case.

INTRAEPITHELIAL CARCINOMA

In view of the difficulty in diagnosis, which has already been discussed, and the fact that in only a proportion of cases does true invasive cancer develop, it is obvious that this condition must give rise to much anxiety on the part of the clinician and pathologist responsible for decision. The anxiety will be the less if the woman is older and has had children. In these circumstances a total hysterectomy together with the removal of a generous cuff of vagina should be carried out. The cuff of vagina must be removed to avoid the chance of recurrence in the vault, as other foci of intraepithelial changes may be present there. The ovaries need not be removed. It is in the case of the younger woman, and particularly when more children are desired, that genuine doubt will arise as to the correct line of action. Apart from receiving from the patient some general expression of opinion as to whether further pregnancies are planned, it seems unfair to expect her to enter the discussion as to whether or not she has cancer or what

should be its treatment. If pathologists and clinicians are not certain about an essentially technical question, how can they expect the patient to be clear in her mind? When intraepithelial carcinoma was first identified as a clinical entity, total hysterectomy was usually advised at any age. Since it has been shown that invasive cancer seems to develop in only a proportion of cases, more conservative methods have been used with the idea of local removal of the tissue, either by amputation of the cervix or by extensive coning of the cervix with the diathermy or even doing nothing and simply observing the case. The patient is then watched and re-examined carefully both clinically and pathologically at regular intervals for years. Amputation of the cervix suffers from the disadvantage that if the case is misjudged, and this can be easy, an early invasive carcinoma can be ineffectually dealt with and lymphatic areas opened up for spread to occur. Coning of the cervix by diathermy at least kills off the carcinoma cells and seals off the lymphatics. In decisions of this order the gynaecologist must be guided by general principles, interpreted in terms of his own experience and attitude.

Although there are reports of such conservative methods being adopted successfully and with the joy of children being borne, I am one of those who feel that if intraepithelial carcinoma is cancer it is difficult not to treat it as such and not to advise hysterectomy. But there must be adequate grounds based upon expert histological examination and adequate biopsy material. It is probable that at present too many 'intraepithelial' carcinomas are diagnosed incorrectly. Another criticism of conservative treatment is that it is not easy to follow up patients who may move about the country and therefore be lost sight of. Although only a third or less may develop true clinical malignancy within ten years, are the results of treatment of the invasive stage so good as to be relied upon when this stage is reached?

Moreover, the invasive growth may not necessarily be 'stage I' when it becomes diagnosed; no-one can predict the speed of spread in the future. It is interesting to note here that Te Linde (1956), who has been one of the American authorities on carcinoma *in situ* ever since its initial recognition as a state, has recently affirmed his belief in hysterectomy as the correct course.

CLINICALLY INVASIVE CARCINOMA

The results of treatment of invasive carcinoma of the cervix, whether by Wertheim hysterectomy or by irradiation only, have been improving with better technique and greater care. They are now so similar—up to 70 to 80 per cent. five-year survivals in stage I—that irradiation remains the standard method of treatment the world over. It is difficult to see that surgery can advance much further, whereas radiotherapy is extending its boundaries by new techniques and methods of dosage control. Today, radium applications are usually reduced to two in number, considerable advance has been made in varying types of applicators, and irradiation of the parametrial tissues will be aided by the cobalt bomb. Further, irradiation gives rise to less risk of ureteric fistula than does operation, and when

the growth has ceased to be confined to the cervix radium is the universally applied first treatment. The results here, too, are improving.

One point which has always remained in favour of the Wertheim hysterectomy has been the question whether the patient who already has glandular involvement will have a better prognosis if operation is performed. This is still difficult to prove because probably the tumour with early gland involvement is more malignant any way, and it is known that if the glands are affected in tumours which prove to be radiosensitive, they, too, may retrogress. Thus, at present, the use of the Wertheim operation in a restricted group of the 'best' cases in stage I or early stage II in fit patients of favourable build for operation is in the nature of a research project to see whether the ten-year survival rates are better than those of irradiation. It may also be justified in certain special instances; for example, if coincident pelvic pathological changes are present in the ovaries or Fallopian tubes.

Operation may be combined with irradiation. If a hysterectomy is contemplated many surgeons now precede the operation by one or more applications of radium with the idea of killing off the growth and sterilizing it. Currie (1952) has performed a magnificent series of such cases, with an 80 per cent. five-year survival rate and a very low operative mortality and few fistulæ.

The alternative method of extensive hysterectomy by the vaginal route (Schauta operation) has not found favour in this country, although Professor van Boudwijk Bastiaanse (1955) of Amsterdam has performed a large series with a 59 per cent. five-year survival rate in stage I and stage II cases, the stage I survival rate being 78.9 per cent. Howkins (1951) devised an extension of the Wertheim operation based upon abdomino-perineal resection. In his operation, in order to minimize the chances of recurrence in the vaginal wall, the whole of the vagina is removed as well as the uterus.

Yet another group of cases deemed fair to be treated by surgery is that in which response to radium treatment appears to be unsatisfactory. This would appear logical although it may well be that such cases are resistant to present-day methods of treatment, either surgical or irradiational. Meigs of Boston has shown in his series (1956) a 61 per cent. five-year survival in stage I and 60 per cent. in stage II cases deemed to have a poor irradiation response and in which radical hysterectomy was then performed. Way (1955) operated on 44 out of 55 radio-resistant stage I and II cases in which the response was judged by Glucksmann's biopsy method: 38.8 per cent. survived five years compared with 10.4 per cent. when given irradiation only.

THE ADVANCED CASE

Exenteration.—Extensive resection of the pelvic organs for advanced cancer of either the cervix or corpus was brought into modern surgery by Brunschwig in 1948. If the uterus is removed, together with the rectum and bladder, the procedure is termed total exenteration. If the uterus, vagina and bladder are removed anterior exenteration has been performed; should

the uterus, vagina and rectum be removed the operation is one of posterior exenteration. In each case deviation of either the urinary flow or of the bowel contents, or of both, has to be provided for.

The primary mortality of the operation is, of course, high. It appears that either the anterior or posterior type of the operation has come to stay; it is doubtful whether there are many cases suitable for complete exenteration. Operations of this type require special facilities, and patients should be referred to centres where these facilities and surgeons experienced in this type of work are available. The disposal of the urine in cases in which the bladder has to be removed has proved unpleasant for the patient if a wet colostomy is necessary, and ureteric implantation into the bowel in any form means the risk of recurrent urinary infections. Modern methods of creating an artificial bladder from an isolated loop of ileum (Bicker, 1952; Pyrah and Raper, 1955) have made a definite advance here.

Other modes of treatment in advanced cases.—Carcinoma of the uterus does not seem to be hormone dependent and, so far as I am aware, operations on the adrenals or pituitary, if tried, have not produced any favourable results. The hope in the future would seem to lie with newer irradiational methods or with chemotherapy.

CARCINOMA OF THE ENDOMETRIUM

Treatment of carcinoma of the uterine body is easier to discuss than that of the cervix. Again there are the possibilities of using surgery or irradiation alone or in conjunction. For many years surgery has been the standard method of treatment where possible, and total hysterectomy together with salpingo-oophorectomy has been performed. Judged by the criterion of five-year survival the results are reasonable and in recent reports vary in different clinics between 60 and 70 per cent. in patients operated on. About three-quarters of the cases seen can have operative treatment so that the end-result, expressed as five-year survival for all cases, is between 50 and 60 per cent. Carcinoma of the endometrium, however, has a longer life history than that of the cervix and therefore in the future the ten-year survival rate may prove a fairer criterion of the success of treatment, certainly in younger patients. For fundal cancer with its limited lymphatic field and relatively infrequent involvement of iliac glands this operation seems to be extensive enough in most cases. Recurrences usually occur in two sites: the vaginal vault or in the vaginal walls, and in the iliac glands; the former is the more common. With the idea of minimizing recurrence various techniques have been developed. For long, surgeons have felt that dissemination of malignant cells may occur at operation by manipulation of the uterus or by the squeezing of growth through the cervix, thus leaving cells to implant in the vaginal vault. Accordingly, steps are always taken at operation to reduce the chance of this happening. The uterus is carefully handled, the cervix is occluded by stitches or a special clamp, and the tubes are also clamped. Implantation can also be prevented by the preoperative use of radium.

An alternative explanation for vaginal recurrence is lymphatic or embolic spread of the cancer. The possibility of this, and also the chance of iliac-gland involvement at the time of hysterectomy, have led some to advocate more radical surgery than the routine total operation combined with salpingo-oöphorectomy. Thus, the removal of a cuff of vagina is practised by many, and others consider that Wertheim's hysterectomy, implying lymphadenectomy, is indicated. It is difficult to see the wisdom of the latter as a routine for a disease in which the lesser operation gives good results even in older and less fit patients. The uterine cavity, however, forms an extensive surface and malignant disease arises not merely in the fundal area; it may also spread from this part downwards. When this is the case, the progress of the disease is akin to that in the cervix and more radical measures are justified. Close upon a fifth of cases of endometrial carcinoma seen at the Radiumhemmet involved the cervix (Kottmeier, 1953). The realization of this possibility has led to the use of fractional curettage being performed to try and assess the extent of the growth before treatment is instituted. Specimens of tissue are taken at successive levels: at the external os, the cervical canal, and in the lower and upper parts of the uterine body. This type of curettage is not always easy of interpretation if there is a large proliferative type of growth present originating from the fundus but forming a large mass in the cavity.

Some patients suffering from carcinoma of the uterine body are older women and may be poor operative risks. These may be treated by radium. In fact, radium has been used in Sweden as the preferred method of treatment for many cases of the disease.

The method used is rather more complicated than that employed for the cervix, and for the best results it entails packing the uterine cavity with multiple sources of radium in 8-mg. applicators, some 10 to 20 being used. In addition, a cervical and vaginal applicator are also put in position. Two treatments are given.

Kottmeier (1953) reported 61.6 per cent. five-year survivals by this method. Unless done expertly, the results of radium treatment are indifferent and not as good as those of operative treatment.

Radium and operation used in combination.—Aiming at the improvement of the end-results of treatment there is a growing tendency, particularly in the United States, to use radium and surgery together. Radium may then be employed either preoperatively or postoperatively. Preoperatively it is applied with the idea of killing the surface growth so that malignant cells are less likely to be implanted at operation. It is also claimed that such insertions reduce the size of the uterus if it is enlarged, and render it firmer so that there is less risk of the uterine wall rupturing at hysterectomy. Total hysterectomy is performed at varying times by different workers after irradiation (one to eight weeks). Some are not impressed by the use of radium in this way because infection may arise and delay operation. If this view is held, radium may logically be used postoperatively by an applicator placed in the vaginal vault two to three weeks after operation.

Corscaden, of New York, has been a protagonist of the combination of radium and hysterectomy, and he and his colleague Tovell (1954) have reported the results of various methods of treatment in their cases. Of 246 cases of endometrial cancer, 57 were treated by intra-cavitary radium \pm x-ray therapy, 62 by operation \pm x-ray, and 127 by preoperative insertion of radium followed by hysterectomy six to eight weeks later. The five-year survival figures were: 33.3 per cent. by irradiation only, 66.6 per cent. by operation, 82.8 per cent. by preoperative radium followed by hysterectomy. Similar results have been reported by Webb *et al.* (1955). Their surgical cases gave a 65 per cent. five-year survival rate, irradiation alone 46 per cent., and radium + surgery 71 per cent. A second five-year follow-up (i.e. 10 years *in toto*) showed that of those surviving the first five years 67 per cent. of the surgical cases survived a second five-year period, 71 per cent. of the radium + surgery patients, and 46 per cent. of the radium cases.

As in so many clinical problems, when statistics are employed in analysis 'things are not always as they seem'. Corscaden and Tovell, in fact, show that if surgery was possible the result of this alone in 'early' favourable cases was an 84.3 per cent. five-year survival rate as compared with 82.8 per cent. in cases treated by radium and hysterectomy, as necessarily the latter were all operable and localized to the corpus uteri. Thus, further work, based upon more accurate details of the stage, site, and type of growth will have to be available for the proper answer to be given to this question.

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THE CYTOLOGICAL DIAGNOSIS OF CARCINOMA OF THE UTERUS

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CYTOLOGICAL examination of the vaginal smear was originally introduced by Papanicolaou (1943) in the United States as an aid to diagnosis of carcinoma of the uterus. It has been generally accepted in the United States where it is employed extensively and it is now being used on an increasing scale in this country.

TECHNIQUE

It is recommended that two smears be examined microscopically in each case.

One is prepared by introducing a pipette into the posterior fornix, and the other by gently scraping the surface of the portio vaginalis of the cervix, especially in the region of the squamo-columnar junction, by means of a small wooden spatula as devised by Ayre (1947). Two films can be made upon glass slides and fixed immediately, while still wet, in a mixture of equal parts of 95 per cent. ethyl alcohol and ether. After fixation the films are stained according to Papanicolaou's method. Alternatively the films may be fixed in Schaudinn's solution and stained by hæmalum and eosin. The use of the spatula is specially directed to the diagnosis of carcinoma of the cervix. A much greater surface of the cervix can be examined in this way than by performing a biopsy. Material may be aspirated directly from the endometrial cavity with advantage if carcinoma of the endometrium is suspected.

There are certain characteristics of malignant cells which distinguish them from normal cells. For example they tend to stain more deeply because the nuclei have a greater affinity for hæmalum. The nuclear chromatin is arranged in thick irregular masses. The size of the nucleus is often larger in relation to the cytoplasm and the nucleoli also are larger than normal. There may be considerable variation in the size and shape. The malignant cells often occur in clumps but may appear singly. They often 'stand out' in the microscopic field. It is generally agreed that if the report on the smear is positive for malignancy this does not constitute a final diagnosis. A positive or 'suspicious' report of malignancy indicates that further examination, probably necessitating biopsy, is required. This will be discussed later.

Considerable accuracy in diagnosis can undoubtedly be attained by cytological examination.

Graham (1953), in Boston, claimed that 90 per cent. and 70 per cent. of cancer of the cervix and cancer of the body respectively can be diagnosed by one cervical smear. Other workers have achieved similar success and Anderson and his colleagues (1953), in Edinburgh, showed an accuracy of 96.4 per cent. for cervical cancer.

The results obtained by most workers in carcinoma of the body are not so good as in the case of the cervix, although recently better results

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have been claimed with smears made directly by aspiration from the endometrial cavity. In the case of post-menopausal bleeding, however, and in suspected carcinoma of the body, it is considered that curettage of the uterus should be performed.

CARCINOMA OF CERVIX

As an aid to the diagnosis of malignant changes in the cervix, cytological examination of vaginal and cervical smears has been found to be a valuable procedure. Only the two most common conditions—squamous cell invasive carcinoma and intraepithelial carcinoma—will be considered here.

Intraepithelial carcinoma of the cervix, to which an analogous condition is found in many parts of the body (e.g. Bowen's disease of the skin), has been and still is a subject of considerable controversy. Many believe that it is really an actual early carcinoma, in which there is no invasion of the deeper tissues and the carcinomatous changes are restricted by the basement membrane. Thus it has been variously termed 'pre-invasive cancer', 'non-invasive cancer', 'carcinoma *in situ*', 'stage 0 cancer'. This lesion shows in small confines all the histological features of a carcinomatous epithelial change just as they are observed in a frank invasive carcinoma.

Robert Meyer (1941) stated that 'the diagnosis can be made when only superficial epithelium is available for study and without the necessity of observing its relationship to the underlying connective tissue'. He regards as criteria for diagnosis certain nuclear and cytoplasmic changes, to which reference has already been made in this article. Other authorities, however, insist that the term 'cancer' should not be used unless definite invasion has taken place, and they prefer to employ such terms as 'atypical' and 'pre-cancerous metaplasia'. The fact that regression and return to normal may take place in some cases lends support to their contention. It is obviously important that the diagnosis should be made in the earliest stages of the disease. The great advantage of the cytological method is that many early and unsuspected cases have been brought to light by it in the first place. The term 'unsuspected' implies that these cases would not have been subjected to biopsy or further investigation were it not for the positive or 'suspicious' report on the vaginal smear.

Graham (1953) reported the results obtained from the cytological examination of 18,303 patients in the gynaecological department at Boston during the period 1943 to 1951.

There were 926 histologically diagnosed carcinomas of the genital tract, of which 469 were invasive cell carcinoma, 86 intraepithelial carcinoma of the cervix, and 206 adenocarcinoma of the endometrium. The numbers clinically suspected in these three groups were 23, 43 and 13 respectively.

Later reports from the literature show an increasing number of cases of intraepithelial carcinoma, of which the great majority are clinically unsuspected. This is due almost entirely to the increasing use of cytological methods. Before the introduction of cytological diagnosis these early lesions

were only found occasionally by biopsy when certain symptoms, such as potting after coitus, led to a suspicion of possible malignancy.

Some authorities (Papanicolaou, 1954; Nieburgs and Pund, 1949, 1950; Reagan, 1952) have described cell patterns which they regard as diagnostic or highly suggestive of non-invasive carcinoma, but this is not generally agreed. I do not consider that, as yet, there are adequate cytological criteria for the differentiation between invasive and non-invasive carcinoma. The cytologist builds up his experience by comparison of the atypical cellular appearances observed in the smears with the appearance found subsequently on histological examination. The following two cases illustrate this point.



FIG. 1.—Smear showing malignant cells of squamous type (Case 1). Hæmalum and eosin ($\times 550$).

Case No. 1.—Mrs. E.H., aged 57 years. 1-para. Menopause 4 years ago. Admitted in July 1956 under the care of Mr. Peel, complaining of pain in the lower abdomen and of bright red vaginal hæmorrhage for four months, and offensive and profuse discharge for three months. She had had chronic bronchitis since 1955. On examination a large central ulcer was found on the cervix. It was friable and bleeding. The vaginal vault was mobile.

A vaginal smear showed large atypical hyperchromatic cells (fig. 1) and a report of squamous cell carcinoma was given. Examination under an anæsthetic was accompanied by dilatation and curettage, biopsy of cervix, and application of radium. The histological report on the biopsy material was: 'a poorly differentiated squamous cell carcinoma of the cervix' (fig. 2, 3).

Case No. 2.—Mrs. K.R., aged 38 years. 1-para. Admitted in July 1956 under the care of Mr. Feroze, complaining of post-coital bleeding for four months. On examination the patient was found to have a fixed retroverted uterus containing fibroids and a reddened cervix. The vaginal smear showed many large atypical hyperchromatic cells considered to represent squamous cell carcinoma (fig. 4).

On examination under anæsthetic, apart from a large Nabothian follicle, the cervix appeared healthy. Normal looking curettings were obtained from the uterine cavity. A large cervical biopsy was taken. Section of the curettings showed normal secretory endometrium. Section of six blocks of the cervical biopsy showed one to contain a focus of carcinoma *in situ* (fig. 5, 6). Total hysterectomy with bilateral salpingectomy and right oöphorectomy was done in September 1956. A mass of adhesions was found in the pelvis. Radial section of the cervix showed, on microscopy, moderate chronic cervicitis and two small areas of carcinoma. There was no evidence of invasive growth.

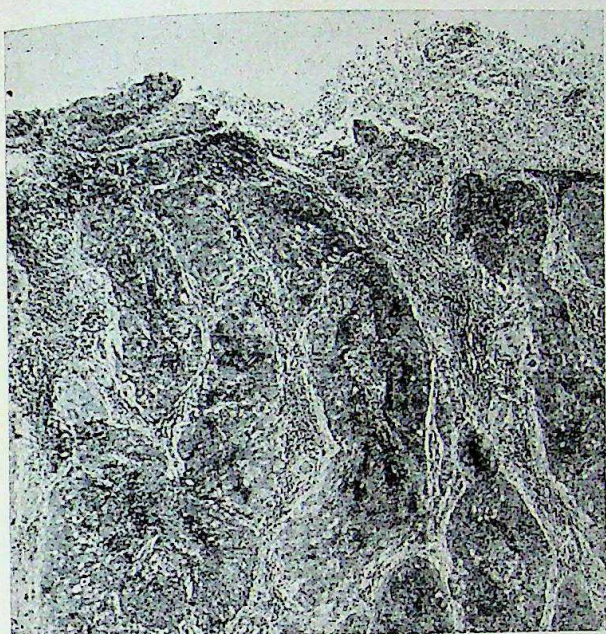


FIG. 2.—Section of portion of cervix from Case 1 showing invasive squamous cell carcinoma. Hæmalum and eosin ($\times 145$).

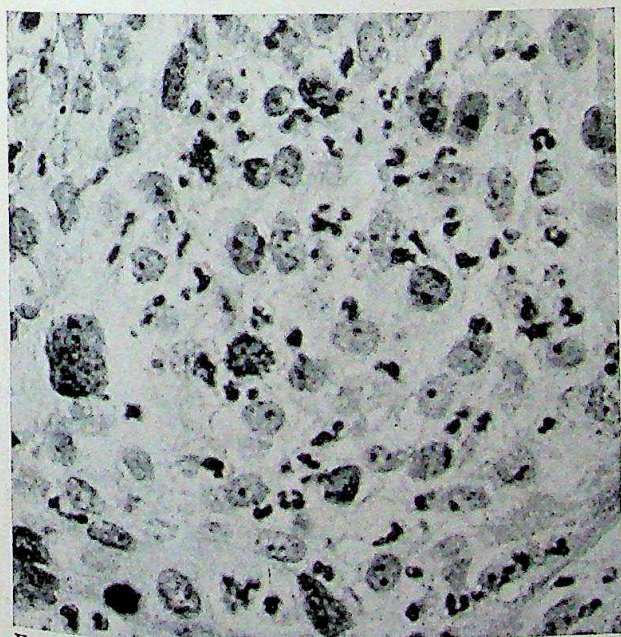


FIG. 3.—Section of portion of cervix from Case 1: compare the cell appearances with those seen in fig. 1. Hæmalum and eosin ($\times 550$).

When atypical hyperchromatic cells of squamous type are observed in the vaginal smear and reported as 'positive', or 'suspicious' of malignancy, the diagnosis can only be established by histological examination and for this purpose it is necessary to perform a biopsy. Excluding certain rare conditions such as carcinoma of the vagina there are three possible alternatives: invasive carcinoma, intraepithelial carcinoma of cervix, and a false 'positive' or 'suspicious' report. In the clinical examination of the patient an obviously suspicious lesion of the cervix, which may be quite small, may be seen by the speculum, a piece taken for examination and a diagnosis established. In some cases no lesion of the cervix is visible, but curettage of tissue from the cervical canal may lead to the diagnosis. Histological examination may reveal a frank invasive carcinoma and in that case there is no further difficulty. Section of the biopsy material,

however, may reveal an intraepithelial type of growth, in which case there may be considerable difficulty, because the extent and the true

nature of the lesion are still in doubt. Examination of serial sections may show invasion through the basement membrane, pointing to an invasive carcinoma. In other cases the presence of invasion may not be determined and the extent of the lesion not appreciated by clinical examination.

A case of unequivocal intraepithelial carcinoma was diagnosed recently by biopsy and treated by amputation of the cervix. A section prepared from a piece of the operation specimen confirmed the diagnosis. The remainder of the cervix was divided into nine pieces, each of which was blocked out for histological examination. In eight of the nine sections areas of intraepithelial carcinoma were found.

The lesion may therefore be multifocal. Further, in a large proportion of these cases there is nothing distinctive about the appearance of the cervix and the gynaecologist may not know where to take a biopsy. A single biopsy may yield non-malignant tissue only. Quadrant biopsies at the squamo-columnar junction as practised by Galvin and his co-workers (1955) have been used by some but have been shown by others to be inadequate. Deep conization of the cervix, which involves the removal of most of the glandular areas of the cervical canal with wide excision of the squamo-columnar junction, is therefore preferred by some authorities, but in a few cases even this procedure fails to remove all the diseased tissue.

False 'positive' and 'suspicious' reports must be considered. Atypical hyperchromatic cells observed in the vaginal smear may be due to inflammatory conditions of the cervix, perhaps associated with infection by *Trichomonas vaginalis* or due to previous irradiation. In some cases biopsy specimens may show an atypical epithelial hyperplasia or a healing erosion. With increasing experience these false reports are reduced to a small number.

Apart from its role in the preliminary diagnosis of malignant disease of the cervix, cytology is concerned also with the management and treatment of patients in whom the diagnosis has been established, more especially with regard to the question of recurrence. In the follow-up of cases of invasive carcinoma treated either by radical surgery or by radiotherapy the



FIG. 4.—Smear from Case 2 showing malignant cells of squamous type. Hæmalum and eosin ($\times 550$).



FIG. 5.—Section from biopsy of cervix in Case 2 showing intraepithelial carcinoma. Haemalum and eosin ($\times 145$).

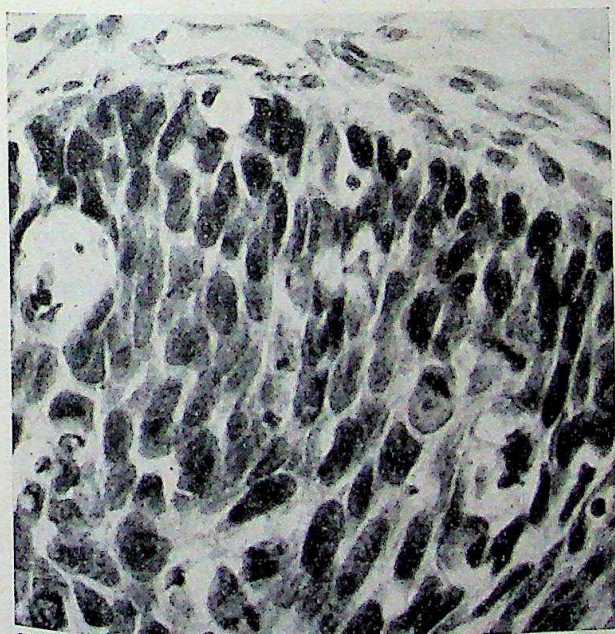


FIG. 6.—Section from biopsy of cervix from Case 2: compare the cell appearances with those seen in fig. 4. Haemalum and eosin ($\times 550$).

vaginal smear is an accurate means of detecting local recurrence. The presence of malignant cells in the vaginal smear following a number of negative reports indicates that the tumour has begun to grow again. It is significant that recurrence can be shown in this way for some time before it can be recognized clinically.

It is impossible to predict what may eventually happen in these cases of intraepithelial carcinoma of the cervix. There is no doubt that many, if left untreated, proceed after an interval varying from a few months to many years to frank invasive carcinoma. Indeed this may follow a total hysterectomy for a small non-invasive lesion. Until the last few years radical measures have been preferred for the treatment of this condition. Recently, however, an increasing number of cases has been reported in which there has been no treatment and in which complete regression has taken place

(Kottmeier, 1953; Petersen, 1956). Some have occurred during pregnancy. The histological diagnosis of intraepithelial carcinoma is usually but not always straightforward. In some cases the biopsy specimen interpreted by

one pathologist as an intraepithelial carcinoma may be regarded by another as an atypical epithelial proliferation not to be considered as potentially malignant. No difference may be detected, however, in the microscopical appearances between a case which becomes invasive and one which does not. Lately there has been a tendency in some quarters to adopt a more conservative attitude, especially in younger patients, with a regular clinical and histological follow-up with biopsies if required. This calls for continued and unremitting care and cytological examination can play an important part.

Adenocarcinoma of the cervix.—As compared with squamous cell carcinoma this condition is of rare

occurrence. The appearances of the malignant cells, which are usually of large columnar type, resemble closely, and are often mistaken for, those found in adenocarcinoma of the endometrium.

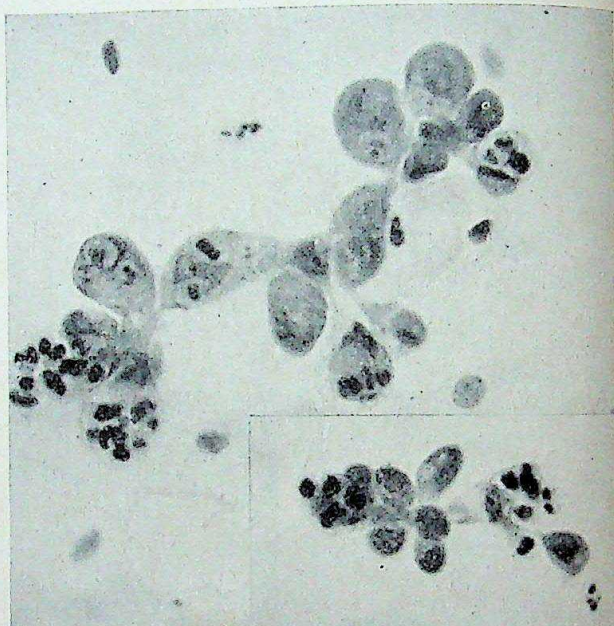


FIG. 7.—Smear from Case 3 showing two groups of malignant cells of columnar type. Note variation in cell size and inclusion of leucocytes. H&E (x 550).

CARCINOMA OF BODY OF UTERUS

In the experience of most workers the cytological diagnosis of carcinoma of the body of the uterus is not so accurate as that of the cervix. Nevertheless, an appreciable number of unsuspected cases is being discovered. It is of interest to note that Wachtel and Plester (1952) found seven unsuspected cases of carcinoma of the uterus in smears from 1,853 cases, of which five were carcinoma of the body and two carcinoma of the cervix.

There is considerable variation in the types of malignant cell found in smears from adenocarcinoma of the endometrium, not only in different cases but sometimes in the same case. The cells may be small, spherical and at times difficult to distinguish from non-malignant endometrial cells. The latter may be present in the vaginal smear in relation to the menstrual period but especially also in cystic hyperplasia of the endometrium. This condition is considered to be associated with hyperœstrinism and the smear usually shows large numbers of superficial epithelial cells from the vagina

in addition to the clumps of endometrial cells. In other cases of adenocarcinoma the cells differ in shape and size and often show a papilliferous appearance like a small bunch of grapes. They may be spherical or oval,

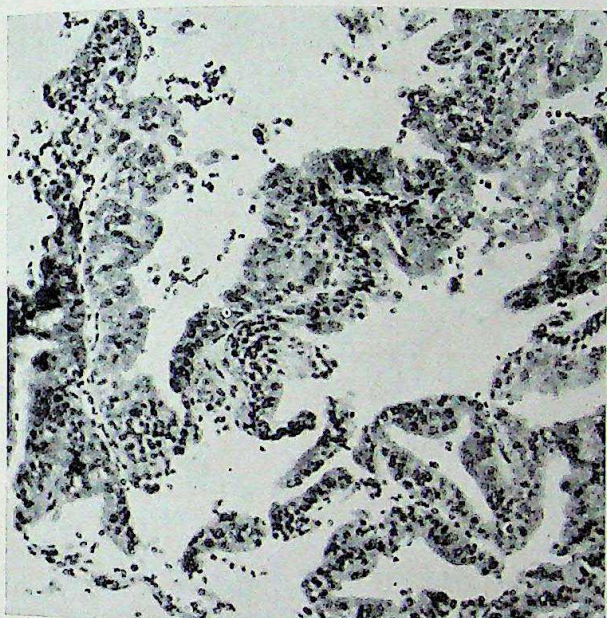


FIG. 8.—Section of curettings from Case 3 showing adenocarcinoma of the body of the uterus. Haemalum and eosin ($\times 145$).

often vacuolated and containing small clusters of polymorphonuclear leucocytes. Even in the same smear there may be considerable disparity in size. These cell characteristics can be verified subsequently in the sections obtained after curettage of the endometrium. In a recent case the vaginal smear showed a number of small cells of squamous type in addition to those typically found in adenocarcinoma, and histological examination showed adenocarcinoma with squamous

cell metaplasia. Some of these features are illustrated in the following case.

Case No. 3.—Mrs. C.W., aged 62 years. o-para. Admitted to hospital on June 27, 1956, under the care of Mr. Peel, complaining of post-menopausal bleeding on and off for the past five years. Examination of vaginal smears showed clumps of malignant cells reported as adenocarcinoma of the endometrium (fig. 7). The following day examination under anaesthetic showed a healthy cervix and a retroverted uterus. Dilatation and curettage were done and histological examination of curettings showed a well-differentiated adenocarcinoma (fig. 8).

On July 5, 1956, hysterectomy was performed, with removal of the Fallopian tubes, ovaries and a cuff of vagina. Section of the uterine wall showed it to be lined with a narrow layer of largely necrotic and partly degenerate adenocarcinoma infiltrating the myometrium for a short distance only.

There is reason to believe that the cytological diagnosis of adenocarcinoma of the uterus can be considerably improved in accuracy by the use of smears obtained by aspiration from the endometrial cavity. Because of the absence of large numbers of cells derived from the cervix and vagina there is less confusion. The malignant endometrial cells, which may be quite small, are less likely to be missed and, as they are likely to be in a better state of preservation, are more easily identified. The difficulty which occasionally arises in distinguishing them from the malignant cells of an undifferentiated squamous cell carcinoma of the cervix is eliminated. Endometrial aspiration has been used during recent years by some cytologists

abroad but it has not yet been employed to any extent in this country.

Hecht (1952), in New York, reported 125 cases in which the endometrial smear was successfully used in the diagnosis of carcinoma of the body. In this study 16 cases of carcinoma were found, six of which had been missed by the vaginal and cervical smears. Varangot and his co-workers (1954), in Paris, examined cytologically 8,525 patients in the outpatient gynaecological department. A vaginal and cervical smear was made in each case. The investigations were always repeated and an endometrial aspiration smear made in addition when the report of the first material was positive or 'suspicious', or when the symptoms suggested carcinoma of the fundus. Sixty-three cases of carcinoma were found: 13 were pre-menopausal and 50 post-menopausal. The false negative error in the first investigation was 25 per cent.; in the second, 9.5 per cent.

A small number of cases has been reported in the literature in which cytology gave a correct positive result when the curettings first obtained proved to be negative. This finding, however, must be exceptional provided the curettage is adequate. At the present it would appear more practical for dilatation and curettage to be done in preference to endometrial aspiration.

In Shelby County, Tennessee, screening for uterine cancer by vaginal cytology has recently been carried out by Erickson and his co-workers (1956) on a very extensive scale.

With the aid of a wide educational campaign and the cooperation of many organizations, over 108,000 women were examined by smears taken by vaginal aspiration. The results revealed 393 intraepithelial and 373 invasive carcinomas, of which 353 and 112 respectively were unsuspected. On the second examination of 33,000 women, 2.2 per 1000 were found to have intraepithelial carcinoma as compared with 3.6 per 1000 on the first examination, whilst the rate for invasive cancer was reduced from 3.4 to 0.3 cases per 1000. The positive and 'suspicious' cases were recommended for further investigation.

As the question not only of treatment but also of the diagnosis and natural history of the disease is still undecided, it would appear preferable to restrict cytology to gynaecological clinics in hospitals where adequate control can be exercised. There are other factors to be considered—the provision of pathological facilities, the psychological effect upon the population in general and the very large expense involved.

I wish to thank Mr. John Peel, F.R.C.S., and Mr. R. M. Feroze, F.R.C.S., for permission to include the clinical details from their patients.

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THE PRESENT STATUS OF HYSTERECTOMY

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'We consider extirpation of the uterus, not previously protruded or inverted, one of the most cruel and unfeasible operations that ever was projected or executed by the head or hand of man. We are very far from discouraging bold or untried operations, but there is a limit beyond which it may not be prudent to go, even should a solitary instance or two of success rise up as precedents to bear out the operator'.

THESE words were written by James Johnson, Editor of the *London Medico-Chirurgical Review* in 1825. Nearly forty years later, in 1863, the great Sir James Young Simpson wrote in relation to vaginal hysterectomy for cancer of the cervix:

'Cases have been put on record where the operation was performed, but with such disastrous results as to hold out no encouragement whatever to its repetition, but rather to serve as loud warnings against it'.

In 1872, Gaillard Thomas reported the results obtained by twelve leading surgeons, including the famous Spencer Wells, in their attempts to perform hysterectomy. They operated twenty-four times with eighteen deaths, and in a later series of eleven hysterectomies performed by six surgeons there was only one survivor. In view of the mortality recorded it is not surprising that there were leaders of the profession who revolted against uterine surgery and both courage and vision were needed to persist against such distinguished opposition, in an effort to make the operation safer.

HISTORICAL REVIEW

The abdominal removal of a uterus for carcinoma had been proposed as early as 1787 by the Professor of Obstetrics at Goettingen, and in 1825 an attempt at hysterectomy was made by Conrad Langenbeck. The patient died several hours after an exploratory incision had been made and the operation abandoned.

Abdominal hysterectomy for fibroids was successfully performed for the first time in June 1853 in Massachusetts. The surgeon was Walter Burnham and his preoperative diagnosis was an ovarian cyst. In spite of this success he considered hysterectomy so dangerous that he decided not to attempt it again. He did not keep this resolution but performed a further fifteen subtotal hysterectomies with twelve deaths. Ten years previously on November 21, 1843, Dr. A. M. Heath, Lecturer in Midwifery at Manchester, successfully completed the first abdominal hysterectomy for fibroids but the patient died from internal hæmorrhage. Three months earlier Dr. Charles Clay, also of Manchester, had attempted a hysterectomy but the patient

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died during the operation. The following year, in June 1844, he removed a uterus with fibroids weighing 24 pounds (11 kg.) together with an ovarian cyst weighing 8 pounds (3.5 kg.) and on the twelfth day, to quote his case record:

'She was doing so well that every reasonable hope was entertained of her ultimate recovery. . . . From the fact of both ovaries and uterus having been extirpated, my interest was doubly excited. On the thirteenth day the nurse put an end to all the flattering prospects by an accident. On lifting her from the bed to ease the bedding the patient fell on the floor, somewhat violently. . . . She died on the morning of the fifteenth day'.

The measure of the success of these surgical pioneers can be estimated by the fact that in less than one hundred years advances in anæsthetic and surgical techniques have made hysterectomy in skilled hands, by either the abdominal or vaginal route, one of the safest of all major surgical procedures. The danger of surgery being advised on occasions without due regard to its possible effect on health and happiness is now greater than the risk of the operation itself.

THE POSITION TODAY

When a mortality of even 2 per cent. or 3 per cent. was regarded as reasonable for hysterectomy it was right that all concerned should consider carefully the case for and against operation before advising or accepting it. In the last twenty years the mortality in experienced hands has been reduced to a tenth of this figure although the indications for operation have been extended; few patients are now rejected as bad operative risks, and more extensive surgical procedures are commonly performed than were considered either advisable or necessary a few years ago. It is perhaps natural therefore that both general practitioners and surgeons should be tempted to underestimate the risks which still exist. Many of the greatest of these are mental rather than physical and for this reason they tend too often to be overlooked. Much unnecessary postoperative suffering is the direct result of the widespread ignorance which persists among patients and their relatives and to a lesser extent among certain members of the profession. For all these reasons the time is ripe for a critical appraisal of the present status of hysterectomy.

All the early abdominal hysterectomies were performed after the abdomen had been opened on the false diagnosis of an ovarian cyst. Encouraged by the success of Ephraim McDowell surgeons felt confident to remove ovarian tumours but soon found that much more formidable and dangerous problems were associated with extirpation of the uterus. When it was attempted the supravaginal cervix was divided and the subtotal operation performed. Diagnosis today is much more accurate and, apart from clinical experience accumulated throughout the years, accessory aids are available. Histopathology, cytology and radiology are all used to varying degrees in preoperative assessment. For example, in clinics where facilities exist for the examination of smears collected as a routine from the cervix of every woman attending

the gynæcological outpatient department approximately 1 per cent. are found to have suspicious changes in the cervical epithelium requiring further investigation. In about one in five of these an unsuspected early cervical cancer is found. Instruments on the principle of the cystoscope have been invented to enable direct examination of the peritoneal cavity, either through the abdominal wall or the posterior vaginal fornix, and although this procedure is not used extensively in British hospitals it is an indication of the constant search for more accurate methods of diagnosis.

There is now little excuse for a high rate of error in preoperative diagnosis. Correct assessment before operation promotes careful consideration of the technique best suited to the particular case and, by removing the element of surprise during operation, adds to the safety of the surgical procedures adopted. In 1932, G. J. Miller, who was head of Tulane University of Louisiana School of Medicine, described hysterectomy as the 'safest of all major abdominal operations' but added:

'It is a successful operation only when it is performed upon the proper indications, a safe operation only when it is performed by properly qualified men'.

Words which were true at a time when most hysterectomies were of the subtotal variety and the mortality was many times what it is today are even truer in 1957. When standards are set high they can be achieved only by work which is consistently good and, as Miller stated so aptly and concisely, preoperative assessment and skilled operative technique are complementary. Both are essential to successful surgery.

In the 1930's a visitor to leading Viennese clinics could see hysterectomy after hysterectomy performed with great skill by the vaginal route. The indications varied from fibroids to functional bleeding, from cervicitis to carcinoma, and although the technique was modified according to the underlying pathology the vaginal approach was the one most commonly employed. At the same time a visitor to the famous Chelsea Hospital for Women, London, would have seen identical patients treated by abdominal hysterectomy with that effortless artistry for which Bonney and his team were renowned. When the question was asked at either centre why the vaginal or abdominal route was selected it was explained by the exponent of each technique that it was simpler, safer and caused less shock. At first sight the replies could not be reconciled but further thought suggested that there was truth on both sides. The vaginal and abdominal operations had been perfected by their respective masters and in their hands, and those of their disciples, each yielded the best results which that particular school could achieve.

Contributory factors are the great differences in the anæsthetic facilities available. Where general anæsthesia was found to be dangerous local was used and many continental surgeons were highly skilled at performing vaginal hysterectomy after local infiltration. In Great Britain today the standard of anæsthesia is generally so high that the type of hysterectomy

best suited to the patient's needs can be planned without being prejudiced by the anæsthetic background.

TYPE OF OPERATION

Many outstanding gynæcological surgeons of the recent past never performed vaginal hysterectomy and some were staunch advocates of the original subtotal operation. This was defended on the grounds that it was less mutilating, easier to perform, safer, and did not shorten the vagina. It was even claimed by some that there was no convincing evidence that carcinoma of the remaining cervical stump was a serious hazard. Undoubtedly many who adopted these views genuinely believed them, whilst others were possibly subconsciously endeavouring to rationalize the technique they practised because of their own inadequate training. An honest surgeon of limited experience in a particular field may declare that in his hands a gastroenterostomy is a safer operation than a gastrectomy, or that a subtotal hysterectomy is safer than either the total operation or vaginal extirpation of the uterus. His declaration should be interpreted as an indication of his personal integrity and operative ability, and not as fair comment on the respective merits of these operations.

SUBTOTAL HYSTERECTOMY

The case against subtotal hysterectomy is now so overwhelming and so generally accepted that the operation is performed less and less frequently. Lewis (1956), for example, records that the incidence of subtotal operations in relation to the total number of hysterectomies performed at the Chelsea Hospital for Women has fallen from 47 per cent. in 1948 to 7 per cent. in 1954. During the five-year period, ending in December 1955, 1,763 hysterectomies were performed in the Oxford area department of obstetrics and gynæcology and, as seen in table I, only 11, or 0.6 per cent., were subtotal operations.

	1951	1952	1953	1954	1955	Total
Total hysterectomy	234	216	253	207	178	1,088
Vaginal "	103	98	127	138	140	606
Subtotal "	5	2	2	1	1	11
Wertheim "	17	9	7	10	15	58
Total	359	325	389	356	334	1,763

TABLE I.—Analysis of hysterectomies performed in the area department of obstetrics and gynæcology, United Oxford Hospitals, 1951-55. There were no operative deaths in this series, and one postoperative death, from pulmonary embolism, a mortality of 0.05 per cent.

From America a similar trend was reported by Johnson and his colleagues (1955) at the annual meeting of the American Association of Obstetricians and Gynecologists. A series of 6,280 consecutive hysterectomies performed

from 1939 to 1954, with an over-all mortality of 0.8 per cent., included 479 subtotal operations, an incidence of 12 per cent. The subtotal hysterectomy had a mortality of 2.7 per cent., but from the year 1952 onwards it was no longer performed by Dr. Johnson and his colleagues at New Orleans.

The old argument that subtotal hysterectomy is safer than the total operation cannot be supported on evidence from the world's leading clinics. It is, in fact, more dangerous, strange though this may seem. It is often stated that the total operation would carry greater risks than the subtotal in those cases in which the latter operation is chosen because of technical difficulties, such as are associated from time to time with extensive endometriosis or chronic pelvic inflammatory disease. The experienced pelvic surgeon knows how to handle these conditions and the technical measures which will make the total operation safe. Where the preoperative assessment is what it should be, these difficult cases are referred to those operators who are equipped technically to deal with them. The figures quoted from New Orleans and Oxford demonstrate this and are typical of the results achieved by many surgeons all over the world.

VAGINAL HYSTERECTOMY

Whilst the subtotal operation is becoming obsolete, vaginal hysterectomy is being used increasingly often. The result is that a progressively higher percentage of uteri are totally removed by the abdominal or vaginal route. Moreover, the number of surgeons who have mastered both techniques, and the number of young surgeons determined to do so, are now greater than ever before and will certainly increase.

Vaginal hysterectomy is most commonly performed when the uterine abnormality is associated with prolapse at or after the menopause, although the more experienced the surgeon becomes in this technique, the more he will use the operation in the absence of prolapse. The practice of performing a Manchester repair and inserting radium into the uterus to control excessive or irregular bleeding has little to commend it and much to condemn it. It has been assessed that the risk of any woman of twenty developing uterine cancer before she dies is approximately 4 per cent. Cervical cancer would occur in 2 per cent. and carcinoma of the corpus in 1.5 per cent. The danger increases with the development of prolonged or excessive bleeding at the menopause and when menstruation continues after the age of fifty. Removal of the uterine body by subtotal hysterectomy does not reduce the risk from cervical cancer, nor does amputation of the cervix remove the dangers of subsequent malignant change in the remaining supra-vaginal cervix or corpus. An incidence as high as 4 per cent. of stump carcinoma has been recorded in large series of cervical cancer cases.

Whilst there could be no justification for removing a healthy organ as a prophylactic measure against cancer, the facts recorded above should be considered when advising treatment involving an unhealthy uterus. If it

requires removal, its complete extirpation will act as an insurance against future trouble, provided that the immediate hazard is not increased by the operative procedure. Furthermore, if in a given patient it is considered that uterine function should cease when a prolapse is repaired, the case for combining vaginal hysterectomy with repair is strong in preference to inducing a radiation menopause with its discomforts and deferred dangers.

Danforth (1941, 1943, 1945) deals with these problems and reports a mortality of 0 per cent. for 440 simple vaginal hysterectomies and 0.6 per cent. for 160 operations combined with a pelvic floor repair. Gwillim (1950) recorded a mortality of 1.4 per cent. in a series of 276 vaginal hysterectomies with repairs, as opposed to no deaths in 104 simple vaginal hysterectomies. In 1955, 245 vaginal hysterectomies were performed without a death in four of the main hospital centres of the Oxford region, and by the end of that year, 1,029 consecutive vaginal hysterectomies had been performed in the Oxford area department with no operative death and one postoperative death from acute pneumonia with heart failure: a mortality of less than 0.1 per cent. When we consider that many of the patients included in this series are old, some of them very old and, because of serious hypertension, diabetes mellitus, or other disease, are not good operative risks, it becomes more apparent that in trained hands the operation by either the abdominal or vaginal route carries such a low mortality that the decision to operate should be determined by the extent of the discomforts or dangers the patient must accept if operation is not performed.

INDICATIONS FOR OPERATION

Most of the conditions for which hysterectomy is advised are benign, as, for example, fibroids, endometriosis, adenomyosis, hormonal bleeding, and chronic pelvic inflammatory disease. Nonetheless, the disability and distress these conditions can often cause make life intolerable for the patient and subject her household to very great strain. When she is in the child-bearing years, if conservative surgery can relieve her symptoms and restore or improve fertility, it should be advised. Myomectomy in carefully selected cases is an excellent example of this, but conservative surgery defeats its purpose if, in spite of fulfilling these requirements, it leaves a useless organ to be a source of future trouble and danger.

The best time to treat uterine cancer is before it occurs. Concerning the place of hysterectomy once cancer has developed, there is some dispute. By general consent carcinoma confined to the corpus is best treated by total hysterectomy with removal of the adnexa, with or without radiation. If the tumour is confined to the corpus the prognosis is good and 70 to 80 per cent. of patients should be cured. Cervical cancer is still treated by radiation in most of the world's centres. There are leading surgeons in many countries who, on selected cases, perform a radical hysterectomy by either the abdominal (Wertheim) or vaginal (Schauta) route, and there are a few

who for some years have been adopting the logical approach of investigating the role of radical surgery combined with extensive radiation therapy. With highly skilled teams the results are encouraging, but it is too early to assess the ultimate value of these procedures.

PREPARATION OF PATIENT

When a woman is told she needs a hysterectomy her fears are often less of the operation itself, or of the reason for it, than of the effect she believes it will have on her. These fears are increased by the foolish attitude of friends and relations and, at times, of her practitioner or consultant. A simple explanation of what is involved given at the right time, namely when the operation is advised, can bring immediate peace of mind and do much to aid full and rapid recovery. The fallacy is exposed of the commonly held belief that with her uterus removed she will no longer be a woman. She must understand that she can do after the operation all the things she did before, except have periods or babies. Her sex life need not be disturbed and in many cases will be enhanced. With hormone therapy available when needed, the change of life, dreaded by so many women, can be easier after a hysterectomy than before. If oestrogens are indicated for subjective symptoms they can be given without the disquieting side-effect of vaginal bleeding.

Ten to fourteen days in hospital, followed by a few weeks of convalescence, and the patient should be able to return to domestic, business, or professional life with renewed vigour. Some will feel well enough to do this in a month to six weeks from the time of operation and the knowledge that this is so should encourage others who require two to three months of slower rehabilitation.

The wise counsel of a sympathetic, but well-informed, general practitioner can be of the greatest comfort and help both before and after hysterectomy. Advances in anæsthetic and surgical techniques have dramatically reduced the operative and postoperative mortality to the low levels now being recorded. Serious morbidity has been decreased in proportion. The patient should be made aware of these facts and all responsible for her care should ensure that no unnecessary suffering, either mental or physical, is endured because of ignorance and unwarranted fears.

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TUMOURS OF THE OVARY AND THEIR MANAGEMENT

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A CLASSIFICATION of ovarian tumours, satisfactory from all points of view, has so far eluded the efforts of numerous authorities. The combined efforts of gynecologists and pathologists have resulted in a variety of classifications, none of which is universally acceptable from the histogenic, pathological and clinical aspects. This confusion is mainly due to our lack of knowledge of the histogenesis of many of these tumours. In addition, in many cases new growths, although of the same origin, may in their development present a variety of characteristics, both pathological and clinical, thus rendering their classification more complicated.

In this short article therefore I make no attempt to classify these tumours, but shall endeavour to tabulate them in a simple manner, mainly from the clinical and practical aspects.

DYSFUNCTIONAL CYSTS

These are commonly called retention cysts. They develop from the Graafian follicles, and small ones may be found in almost every ovary.

(1) *Follicular cysts* develop from a follicle which has failed to rupture. They may be found in association with fibromyomas, metropathia hæmorrhagica, a previous oöphoritis and occasionally with hydatidiform mole and choriocarcinoma.

(2) *Corpus luteum cysts* develop from the corpus luteum and are seldom seen apart from pregnancy. In cases in which there is excessive production of gonadotrophic hormones, e.g. hydatidiform mole, granulosa lutein cysts are often found. They differ from the corpus luteum cysts in that the luteinization affects the granulosa and theca interna cells, and the granulosa layer is thin and not convoluted.

These retention cysts are not true tumours; the lining epithelium is flat and not proliferated. They are often bilateral and multiple, but seldom exceed one inch in diameter. They sometimes cause pain due to the tension produced in the ovary, especially in sclerosis following perioöphoritis. They tend to disappear spontaneously and rapidly, and the treatment is expectant. The patient, however, should be examined at bimonthly intervals as, short of laparotomy, the diagnosis is never quite certain, and a new growth may be developing.

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OVARIAN TUMOURS

The structure of the ovary is very complex and, in addition, it may contain small inclusion cysts and cell nests of embryonic origin (Walthard, 1903). Tumours of the ovary may arise from any of the structures present and so we find a great variety of growths of histogenic, pathological and clinical interest.

TUMOURS OF EPITHELIAL ORIGIN

(1) *Cystoma simplex*.—This cyst is unilocular and almost always unilateral. Lined by a single layer of ciliated epithelium, it contains straw-coloured fluid and seldom grows to a large size. It is not malignant.

(2) *Serous papillary cystadenoma* closely resembles the cystoma simplex. The serous fluid content is also the same. The lining epithelium is identical: cuboidal, ciliated and similar to that of the Fallopian tube. Both are believed to arise from Walthard inclusion rests. The cyst is usually multilocular and is bilateral in about a third of the cases. It sometimes grows between the layers of the broad ligament, thus becoming fixed in the pelvic cavity and presenting difficulty in removal. It seldom attains a large size. Papillomas abound on the inner, and often on the outer, surface. These papillomas may appear as flat warty growths, in which case they are supposed to be stationary; or they may be villous in type, when they are actively proliferating. The latter type has a marked tendency to become malignant. In some cases papillæ are to be found on the outer surface of the tumour and on the pelvic peritoneum, giving rise to ascites. These are not necessarily malignant, as the peritoneal papillæ are alleged to be due to metaplasia rather than to implantation; they disappear following removal of the cyst.

(3) *Pseudomucinous cystadenoma*.—This is easily the commonest tumour of ovarian origin and may occur at any age. It is the largest and may fill the whole abdominal cavity. The cyst is multilocular, the loculi varying in size. The surface is smooth, but lobulated and of a pearly-grey colour. The loculi are lined by a high columnar epithelium which secretes a thick pseudomucin. The tumour feels cystic over the large loculi and semi-solid over the small loculi. The septa between the loculi often break down, but the capsule seldom ruptures. Papillary growths may be found in the cavity, but are usually benign. Malignant change, however, occurs in about 7 per cent., is usually found in the more solid areas and may perforate the capsule. The incidence of malignancy increases with the age of the patient. The tumour is unilateral in about 93 per cent. of cases. In its development it usually rises up into the abdominal cavity with a long broad pedicle. A considerable portion, however, may remain in the pelvis. The rate of growth varies, but rapid increase in size always suggests the possibility of malignant change.

Occasionally, in rapidly growing tumours, the capsule may give way, and actively secreting cells may become implanted on the peritoneum and abdominal organs, giving rise to the condition of *pseudomyxoma peritonei*. The abdomen becomes filled with thick gelatinous pseudomucin, the intes-

tines become involved, function of the abdominal organs is interfered with and the patient eventually dies. In rare cases the condition may spread to the pleura. The abdomen may be opened repeatedly to remove the gelatinous material: this will relieve symptoms and may prolong life. There is some doubt (Shaw, 1955) as to the true origin of this condition, at least in certain cases, as it is often found in association with mucocele of the appendix or carcinoma of the large intestine and is more common in men than in women.

MALIGNANT TUMOURS OF EPITHELIAL ORIGIN

These tumours are usually carcinomas and the incidence, according to Shaw (1932) is 25 per cent. of all ovarian tumours but, according to Corscaden (1956) it is only 15 per cent. Ovarian cancer may be primary or secondary, the primary growth being the more common. They may occur at any age, but occur more often in patients over forty.

Malignant adenocystoma.—This is the commonest malignant tumour of the ovary. It does not grow to a very large size, and is bilateral in about 35 per cent. of cases. It is usually serous in type, with numerous papillae and solid areas. The latter are often necrotic, and rupture or perforation of the cyst wall occurs early. This results in the rapid formation of generalized abdominal deposits and ascites. The tumours become firmly fixed and often give rise to the 'frozen pelvis'. The disease is often far advanced before the onset of symptoms. Following treatment, the absolute survival rate is about 20 per cent. (Pearse and Behrman, 1954).

This cyst closely resembles the serous papillary cystadenoma and has the same origin. Believed to be malignant from onset, its chief characteristics are its tendency to be bilateral, the very numerous papillae, the solid necrotic areas, early perforation of the wall, fixation and associated ascites. It is one of the most dangerous tumours found in women.

Primary adenocarcinoma.—There is some confusion in the classification of this tumour, as certain authorities include all primary carcinomas, including cystic forms, under this heading. There is, however, a primary adenocarcinoma which is usually dense and solid, but which occasionally may contain some loculi. It has a smooth, lobulated surface, is pedunculated and is often bilateral. Ascites, often serous, may be present. The capsule may break down and secondaries may be found as far away as the liver and pleura. Fixation in the pelvis may develop later. Fluid withdrawn from the abdomen or pleura may reveal cells of malignant ovarian origin.

Metastatic ovarian carcinoma is usually an extension of malignant disease from the stomach, colon, breast or uterus. The malignant cells may travel by any of the usual channels and are also believed to metastasize via the peritoneal fluid. Both ovaries are usually involved, and the primary growth may be very small and difficult to locate. The tumours may appear some years after the removal of the primary growth. They can attain quite a large size, often contain loculi, and tend to become necrotic and adhere to sur-

rounding structures. Serous ascites is usually present, especially in advanced cases. On microscopic examination they closely resemble the primary growth.

The Krukenberg tumour (Krukenberg, 1896) is believed to be due to retrograde lymphatic spread from the stomach, but the primary may in some cases be found in the intestine or uterus. It presents bilateral growths resembling other metastatic ovarian carcinomas. Peritoneal metastases are not common, but ascites is usually present. Histologically, the distinguishing feature is the large mucinous epithelial cell with the nucleus flattened at one side: the so-called 'signet-ring' cell. Novak (Novak and Gray, 1938) believes that this tumour may occasionally be primary in origin.

TUMOURS OF CONNECTIVE TISSUE ORIGIN

Fibroma is not uncommon. It consists of bundles of spindle-shaped cells and dense fibrous tissue. It is usually unilateral and may attain a large size. If small, it may appear as a small papillomatous growth on the surface of the ovary or it may occupy a considerable portion of the ovary. The large variety replaces the entire ovary. The surface is smooth and the shape oval. It is pedunculated and liable to undergo torsion. Large ones show degenerative changes, with cystic spaces and sometimes calcification, just as in uterine fibroids. Although the tumour is benign, ascites is recorded in 20 per cent. of cases, but Biggart and Macafee (1955) found it in 32 per cent. Hydrothorax (Meigs, 1954) may also be present. This combination of findings, known as Meigs', or the Demons-Meigs, syndrome, may also occur with other ovarian tumours or cysts and in cases of injury to or carcinoma of the pancreas.

Sarcoma is rare. It is most frequently of the round-celled type and many variations have been described. It is difficult to differentiate histologically from some of the special tumours. It is said to occur most commonly about the time of the menarche and the menopause. It resembles the fibroma, but is often bilateral. The prognosis is very grave.

TERATOMAS

The origin of these tumours is unknown. There are two forms: (1) The dermoid, which is almost always benign; (2) the solid teratoma, which is essentially malignant.

The *dermoid cyst* is relatively common. It may be found at any age, is usually unilateral and unilocular, oval in shape with a smooth surface. Its greatest diameter seldom exceeds six inches (15 cm.). It is often found lying either in the pouch of Douglas or in front of the broad ligament. It may sometimes be found incorporated in a pseudomucinous cystadenoma. The wall of the cyst is lined by squamous epithelium, but columnar or cubical epithelium is also present in places. One area of the wall is greatly thickened and projects into the cavity. This area contains hair, teeth, bone, cartilage, intestinal structures and sometimes thyroid and other glands.

Sex glands are never present. Hair follicles, sebaceous and sweat glands are present and the thick fluid content is of sebaceous origin. The various structures found are adult in character. The term 'dermoid' is therefore incorrect, as the tumour contains tissue from all three layers of the embryonic phase.

This cyst grows slowly, may not cause symptoms for a long period and because of its lengthy pedicle is liable to undergo torsion. Malignant change occurs in about 4 per cent. of cases.

The *solid teratoma* is a very rare but highly malignant tumour. It appears usually in patients under thirty years of age. Of small to moderate size, it is ovoid, irregular in outline and bilateral in about 25 per cent. of cases. Ascites and adhesions are often present. The cut surface appears fleshy and trabeculated with a gelatinous base, with occasional loculi. It contains almost every type of embryonal tissue, very mixed up and without any attempt at arrangement. The malignant tissue is often sarcomatous.

Struma ovarii (thyroid tumour of ovary).—Thyroid tissue is often found in a teratoma and in some cases may be the chief constituent of the tumour. When the thyroid tissue is dominant the term 'struma ovarii' is applied. In a small percentage of such cases the thyroid tissue may be so functionally active as to produce symptoms of thyrotoxicosis. These tumours should be considered malignant, many showing carcinomatous change.

TUMOURS ORIGINATING FROM PRIMITIVE MESENCHYME

These are relatively rare, but are of great embryological and pathological interest. Most of them appear to secrete hormones which affect the genital tract. Two have a feminizing, and one a masculinizing influence.

FEMINIZING

(1) *Granulosa-celled tumour*.—The origin of these tumours is still controversial. There is often a mixture of granulosa and theca cells, one or other type being predominant. A greater or lesser degree of luteinization is often present. These tumours occur most commonly over the age of 40 years. They secrete oestrogen and give rise to uterine bleeding. They are usually unilateral; if bilateral they are more likely to be malignant. They are not of large size, are encapsulated and solid, but may contain cystic spaces.

(2) *Brenner tumour*.—This tumour is often found in the wall of a pseudomucinous cyst or may appear independently and resemble a fibroma. It contains epithelium which is transitional in type and secretes a hormone which affects the endometrium, usually producing glandular cystic hyperplasia. It seldom appears before the menopause and is always benign.

MASCULINIZING (VIRILIZING)

The *arrhenoblastoma*, or virilizing tumour of the ovary, is very rare and usually appears before the age of thirty. It produces virilizing changes which disappear after its removal. Amenorrhœa is a characteristic symptom. The tumour is usually unilateral and often malignant. Histologically the cells

are mixed in type and, if poorly differentiated, are not virilizing. According to Laffargue (1955), the Leydig cells are more masculinizing than the Sertoli cells.

NEUTER

Dysgerminoma.—This rare tumour usually appears in adolescent or young women. It is solid, greyish white in colour, mobile, and often bilateral. It does not secrete sex hormones. It often attains quite a large size and is usually malignant. Ascites is seldom present. It corresponds to the seminoma of the testis and is supposed to originate from the primitive undifferentiated mesenchyme.

CLINICAL FEATURES AND DIAGNOSIS

Ovarian tumours are usually silent, especially in the early stages of development. The patient may complain of vague abdominal symptoms of a gastrointestinal type. Since the tumour may reach a size of 15 cm. in diameter before it is readily palpable abdominally, the importance of a bimanual pelvic examination in such cases need not be emphasized. The large benign cysts attract attention usually by the distension only, but if very large may cause cachectic symptoms. Most ovarian tumours, except the rare ones which secrete hormones, have no effect on menstruation, even when bilateral and very advanced.

Pain is not a frequent symptom, but if present it may indicate torsion of the pedicle, hæmorrhage into the tumour, adhesion to surrounding structures, rupture or infection. Vague pelvic discomfort is not uncommon. A tumour impacted in the pelvis may give rise to pressure symptoms and cause retention of urine. Pressure on the veins at the pelvic brim may cause œdema of the legs, whilst a very large cyst may cause respiratory embarrassment.

The identification of an ovarian tumour is often easy, but by no means always so. Obesity, a rigid abdomen, ascites and the presence of other pelvic or abdominal swellings may make accurate diagnosis difficult. Examination under anæsthesia is sometimes necessary. A small ovarian enlargement will be found deep in the pelvis to one or other side. A larger tumour may occupy the pouch of Douglas. If the tumour has risen out of the pelvis and is not very large it may be found laterally, situated in the lower abdomen. Larger tumours usually lie centrally in the abdomen. Most ovarian tumours are smooth in outline, but pseudomucinous cysts are often irregular. An ovarian tumour may feel almost entirely cystic, but solid areas can often be identified. They are usually tense and easily outlined, but infrequently may be so flaccid as to simulate ascites. It is important to determine whether the condition is unilateral or bilateral, but this is sometimes impossible in the case of large embossed tumours. Solid tumours are usually much smaller than the cystic variety and are easier to outline. They feel firmer and harder, but they may contain small cystic areas.

DIFFERENTIAL DIAGNOSIS

A full bladder can readily be excluded. A pregnant uterus may occasionally give rise to difficulty and lead to error in diagnosis. The soft enlarged uterus resembles an ovarian cyst in many ways, but other signs of pregnancy can usually be found. Breast changes have been found with some ovarian cysts. The detection of intermittent uterine contractions, x-ray examination and a positive pregnancy test will put the matter beyond doubt.

Uterine fibromyomas are hard and firm, but large ones may have areas of cystic degeneration. They usually move with the cervix and the uterus cannot be identified separately.

An ectopic pregnancy usually causes acute symptoms, and the recent history will suggest the cause. Hydrosalpinx and pyosalpinx are usually fixed and tender, and here again the history will be of great help and laboratory investigation may point to an infective cause. It is always important to ascertain whether ascites is present and the possibility of a pleural effusion should not be overlooked. If either is present, some of the fluid should be aspirated and the examination of the cellular content may indicate the true nature of the tumour. Greater difficulty in diagnosis may be experienced in the differentiation of enlargement of the spleen, kidney tumours, large pancreatic cysts and encysted tuberculous peritonitis, when more prolonged and detailed investigation may be found necessary to arrive at a correct diagnosis.

Having diagnosed the presence of an ovarian tumour, it is desirable to determine, when possible, the nature of the tumour. This is not often possible with certainty but, being mindful of the various characteristics already described, a fairly accurate diagnosis can often be reached. It can usually be determined whether the tumour is solid or cystic, unilateral or bilateral. Age incidence is not of great help, as there are so many exceptions to the general rule.

The most important consideration is whether the condition is benign or malignant. Of all ovarian tumours 75 per cent. are benign and 25 per cent. are malignant (Shaw, 1955). Malignant tumours are bilateral in 75 per cent. and benign tumours are bilateral in 16 per cent. of cases. Local symptoms of pain and pressure are more common in malignant cases, and occur earlier. Ascites, post-menopausal bleeding and rapid enlargement are much more frequent with malignant growths. Whilst bilateral œdema of the legs may result from simple pressure, unilateral œdema is strongly suggestive of malignant invasion of the pelvic veins. Early fixation in the pelvis and nodular masses felt in the pouch of Douglas are indicative of malignancy. X-ray examination will reveal teeth of bony formation in a dermoid. Cachectic changes in malignant cases are not uncommon, especially in young patients.

COMPLICATIONS

Torsion of the pedicle of an ovarian tumour to a greater or lesser degree occurs in some 10 per cent. of cases. Congestion and perhaps hæmorrhage

into the tumour may ensue, with accompanying pain, peritoneal irritation and the usual acute symptoms. If untreated, adhesions form. These cases usually require immediate surgical intervention. Rupture may be sudden or gradual. In the latter case there are few or no symptoms, the tumour becomes more difficult to feel, the peritoneal fluid is encased and papillary growths may develop on the peritoneum. Sudden rupture causes acute abdominal symptoms which usually subside in a short time. Infection of the tumour is seldom seen. It may arise from a salpingitis, adhesion of the bowel or during the puerperium.

An ovarian tumour is occasionally discovered during pregnancy. The earlier in pregnancy the examination is made, the easier it is to identify the tumour. In addition to the usual complications the tumour may cause abortion, pressure symptoms and/or malpresentations. During labour it may obstruct labour, undergo rotation or rupture. Infection is an added complication likely to arise during the puerperium.

TREATMENT

A small cystic enlargement of the ovary, found during a pelvic examination, may be a simple retention cyst which does not require treatment. Frequent examination should be carried out to note whether the swelling disappears or increases in size. If enlargement is observed, it is most likely a tumour.

If ascites or hydrothorax is present, the examination of the fluid may reveal important information as to malignancy. Paracentesis should be performed carefully to avoid puncturing the tumour and thus disseminating its contents. The safest method of obtaining ascitic fluid is through a small sub-umbilical incision.

Ovarian tumours should be removed without delay. With the abdomen opened, the experienced operator will be able to decide, with a fair degree of accuracy, whether the condition is benign or malignant. As a general rule, if the patient is over 40 years the safest treatment is the removal of both ovaries and tubes together with total hysterectomy.

In the younger patient it is very desirable to be more conservative. The presence of ascites is not conclusive of malignancy: it may, for instance, occur with a fibroma. Papillary growths on the peritoneum may disappear following removal of the tumour, especially the flat, warty type. Villous papillomas are more likely to be malignant. Bilateral dermoids are usually benign, as are pseudomucinous and serous cysts. These growths can be shelled out or excised, leaving some healthy ovarian tissue which will carry on normal function. Endometrial cysts are easily recognized by the pearly appearance, the dense adhesions and the chocolate-like contents. Again, surgical treatment should be conservative in the younger patient. If only one ovary is involved, the apparently healthy ovary should be carefully examined and, if necessary, incised to outrule bilateral tumours. If the tumour is malignant the treatment should be radical, irrespective of the age

of the patient.

Tapping of ovarian cysts is not practised nowadays except in those rare cases of patients who are medically unfit for operation. Tapping should be avoided during the removal of a cyst, but is occasionally found necessary in very large cysts and in the presence of adhesions. In such cases, aspiration of the fluid should be carried out without dissemination over the peritoneum or abdominal incision.

During pregnancy an ovarian tumour should be removed as early as possible. If discovered in the later months and if solid it should be removed without delay. If, however, it is cystic, it is likely to be benign and labour can be awaited. If in the pouch of Douglas, it may be possible to push it upwards into the abdominal cavity above the presenting part. Care should be taken to avoid rupturing the cyst during any manipulations associated with labour. It should be removed abdominally within forty-eight hours of the end of labour. If it obstructs delivery and cannot be displayed upwards, Cæsarean section should be performed followed by removal of the cyst. It should not be aspirated from below to allow of a vaginal delivery.

The supplementary treatment of malignant ovarian tumours calls for serious consideration. If a tumour is found to be malignant at biopsy, should the abdomen be reopened for the purpose of removing the remaining ovary and uterus? According to Corscaden (1956), these secondary operations do not improve the prognosis if the original operation was properly performed and involvement of the remaining ovary excluded. The value of deep x-rays following removal of a malignant growth is still controversial, but there is evidence that such treatment does prolong life, especially if high voltages are used. Holman (1955) has shown that malignant ovarian tumours of embryonic origin have a much better prognosis than adenocarcinoma and that many of them are sensitive to deep radiation. It would appear therefore that deep radiation is a desirable supplementary treatment except in the advanced inoperable condition, where it may shorten life.

The use of colloidal gold is helpful in retarding the reaccumulation of ascitic fluid, but a beneficial effect on the cancer has not been demonstrated.

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THE MANAGEMENT OF LEUCORRHŒA

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LEUCORRHŒA, meaning literally 'white discharge', is a term generally used nowadays to describe all genital discharges not containing blood. It is essentially a symptom with causes ranging from simple excess of normal secretion to grave local disease. Before treatment is begun it is imperative that the source and cause of the discharge be determined. To achieve this, some knowledge of local genital physiology is helpful.

NORMAL SECRETIONS

Between puberty and the menopause, normal secretions from the cervix and vagina provide a 'defence mechanism' against ascending infections. The thick squamous epithelium of the vagina (containing no glands), under the influence of œstrogens, contains much glycogen, which by Döderlein's bacilli is converted into lactic acid. Hence the normal vaginal transudate has a pH of about 4.5: i.e. on the acid and protective side. Superficial desquamation adds epithelial cells to this transudate causing its white opaque appearance. Before puberty and after the menopause, deficiency of œstrogen entails thinning of the vaginal epithelium, containing little glycogen. Thus the pH is raised to the alkaline side, predisposing to infection. The cervix, profusely supplied with glands, produces alkaline mucus which plugs the cervical canal and protects the upper genital tract against infection. Removal of this plug at menstruation, abortion, or labour may open the way to ascending infection. The vulnerability of the lower strait before puberty and after the menopause, and of the upper strait at menstruation and following abortion or labour, will thus be obvious.

Bartholin's glands only produce a thin alkaline mucus under erotic stimulation. The corporeal endometrium and the epithelium of the Fallopian tubes produce no appreciable secretion under normal conditions.

CLINICAL INVESTIGATION

History.—The history should entail an inquiry into general health, hygiene, and habits, especially in adolescence. Age is significant in relation to puberty and the menopause. Marriage may introduce the factor of local irritation and infection. Parity, whether full-time or abortion, increases the possibility of infection and trauma. Change of menstrual habit, relation of discharge to loss, and the incidence of congestive dysmenorrhœa may be significant. A sudden onset of discharge and a short history are more

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significant than a gradual onset and a long history. Quantity can be judged by the necessity to wear sanitary protection. The presence of vulval soreness or pruritus must be noted. Odour is chiefly valuable as an objective sign. *Blood staining, however slight, introduces serious possibilities demanding urgent investigation.* Character or colour is often inaccurately described by the patient. As an objective sign, however, it is the most satisfactory basis of classification of the various causes. Dyspareunia, frequent or painful micturition, and low backache are noted (fig. 1).

Examination.—This begins with an assessment of the *general condition*, with special reference to anæmia and organic disease, and includes abdominal examination for tenderness or swelling in the hypogastrium.

Local examination is systematic, beginning at the vulva (fig. 2). Redness or irritation of the skin, or atrophic changes in the vestibule or introitus should be noted. Infection of the urethra or of Bartholin's duct demands bacteriological investigation, especially for gonococci. The amount and nature of the discharge at the lower vagina are noted. Further examination is influenced by the age-group of the patient.

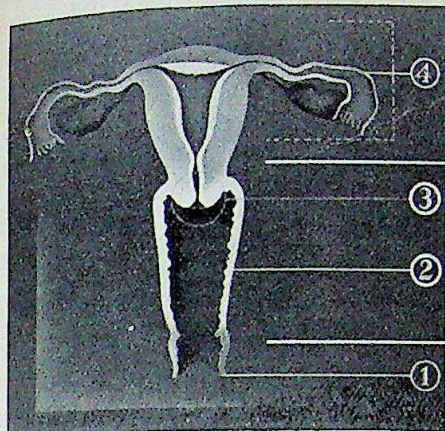
Before puberty foreign bodies and gonococcal infections must be kept in mind. The former give rise to a yellow, sometimes blood-stained, discharge which later may become offensive. A foreign body may be palpable on rectal examination, but vaginal speculum examination under anæsthesia is ultimately required for confirmation and removal. The secondary infection will require appropriate treatment. Gonococcal infections cause a profuse purulent, irritant discharge associated with vulvo-vaginitis (see under 'purulent discharge').

Occasionally infection in these cases is due to coliform organisms, staphylococci, or diphtheroids. Smears, culture, and tests for sensitivity will give guidance for treatment by the appropriate preparation. In coli infections, the urinary tract is investigated. In all pre-pubertal infections, small doses of œstrogens, in the form of stilbœstrol, 0.1 mg. twice a day for ten to fourteen days, are a valuable adjuvant to treatment, as this stimulates the vaginal 'defence mechanism' previously referred to.

During the reproductive phase, a simple, non-irritant, white discharge only requires further investigation if resistant to simple general treatment. Such cases may require cauterization of a cervical erosion. All purulent or thick white discharges call for full investigation. The unmarried woman should



FIG. 1.—To illustrate how proximity of the infected cervix and upper vagina to the bladder and parametrium can produce dysuria, dysmenorrhœa, dyspareunia and backache.



④ Upper strait: Ascending infection, following abortion, childbirth and, rarely, gonorrhœa.
Descending infection occasionally from appendix, diverticula, or tuberculosis.

③ Cervix: 'Non-malignant unhealthy cervix'.—Erosion, cervicitis, ectropion, polypi.
Malignant cervix (always to be kept in mind).

② Vagina: Trichomonas. Monilia. Foreign bodies. Coli and diphtheroids. Senile. Gonococcal (prepuberty). Douches.

① Vulva: Urethritis. Bartholinitis. Secondary vulvitis (e.g. trichomonas, monilia, any purulent discharge).

FIG. 2.

be referred to hospital. In the married woman, a speculum with neutral lubricant should be used, the discharge examined bacteriologically, and the vaginal walls inspected. The cervix is displayed, any discharge in the canal is collected for smear and culture; any scars, erosion, ectropion, polypi, or ulceration are noted, and tested for 'contact bleeding' and friability. Finally, the uterus, Fallopian tubes, ovaries, and cellular tissues are examined bimanually for position, mobility, tenderness or thickening.

At and after the menopause, any discharge of recent origin, whatever its nature, suggests the possibility of malignant disease. Full investigation with this in mind is therefore imperative in all cases.

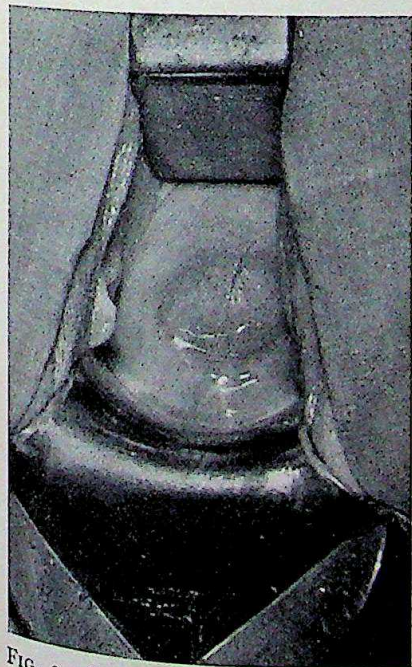


FIG. 3.—Simple erosion of the cervix with mucoid discharge.

THIN, WHITE, NON-IRRITANT DISCHARGE

This is a simple excess of normal secretion, occurring chiefly in adolescence but occasionally persisting. General causes are anæmia, lack of exercise and fresh air, and inadequate diet. Local causes are congestive states produced by constipation, pregnancy, erotic stimulation, contraceptives and douches. Occasionally the body of the uterus may be retroverted or contain fibroids—or the cervix may show a simple erosion possibly associated with excessive oestrogen action. Microscopic examination reveals no pathogenic organisms or pus cells, but an abundance of desquamated epithelial cells and some mucus.

Treatment.—Mild cases require

nothing more than general tonic measures, hygienic advice, and reassurance. More severe cases call for examination of the cervix and cauterization of an *erosion* (fig. 3) if found. Hormones are ineffective, and douching should be forbidden.

The thick white discharge of moniliasis is discussed in a later section (p. 313).

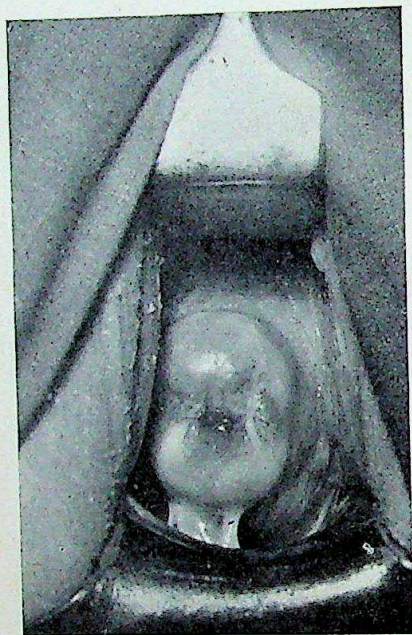


FIG. 4.—Chronic endocervicitis. Thick, muco-purulent discharge exudes from the external os. Secondary erosion on posterior lip.

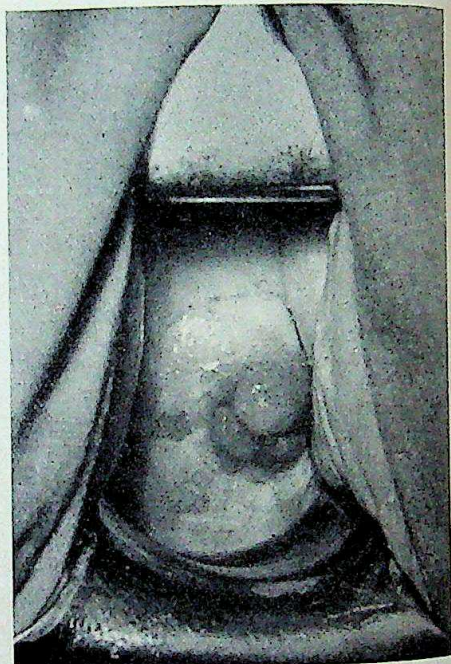


FIG. 5.—Chronic cervicitis. Thickened cervix with polypi and Nabothian follicles.

MUCO-PURULENT DISCHARGE

This arises primarily from various cervical lesions. In long-standing cases, a secondary vaginitis may supervene. The term '*non-malignant unhealthy cervix*' includes two conditions:—

In *chronic endocervicitis* (fig. 4) the mucous lining is infected, and muco-pus exudes from the external os, often producing a secondary erosion, which appears as a bright scarlet area of columnar epithelium which has replaced the normal squamous layer. Mucus polypi may develop.

In *chronic cervicitis* (fig. 5) the infection has spread to the mucus glands and fibromuscular tissue. Deep fibrosis results in thickening and hardening of the cervix, and in occlusion of some ducts. The distal portions of these glands form cysts containing muco-pus, some of which project on to the vaginal surface of the cervix (Nabothian cysts or follicles). Infected fibrosed scars of old lacerations resulting in *ectropion*, appearing like an erosion, are often present. Erosions, ectropion or polypi may cause 'contact bleeding' or blood-stained discharge. Infection in these cases has usually resulted

from childbirth, abortion, operation, or long-standing prolapse. Concomitant urethritis may raise suspicion of gonococcal infection, and demand cultures from the cervical canal and the urethra. Usually, microscopic examination of the discharge reveals many pus cells, much mucus, and a great variety of organisms.

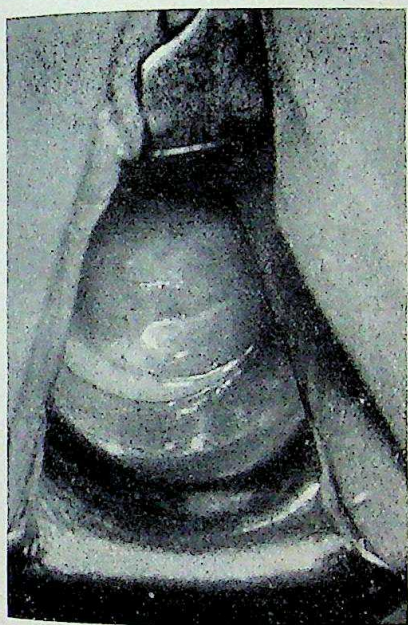


FIG. 6.—*Trichomonas* infection. Profuse, thin discharge with 'strawberry' patches on the vaginal surface of the cervix and in the fornices.

Treatment.—Every cervical erosion must be regarded with suspicion, and carcinoma, invasive or non-invasive, must be eliminated before local treatment is undertaken. Papanicolaou smears followed by biopsy may be required. Hence all but the simplest erosions must be dealt with in hospital. When malignancy has been eliminated, cervical erosion and ectropion may be treated by actual cautery, diathermy or conization. Repair of tears and ectropion (trachelorrhaphy) is rarely attempted nowadays, but amputation may be required for severe cases. Polypi are removed by torsion, the base cauterized, the body of the uterus curetted, and all material is submitted for biopsy. All cervical operations, even simple cautery, require skill and experience if damage and complications are to be avoided.

PURULENT DISCHARGE

Trichomonas vaginitis (fig. 6) is the commonest cause, giving a profuse, yellow or green, slightly frothy, discharge with unpleasant smell. Occasionally it is paler in colour. The vagina is deep red with prominent, congested papillæ giving a so-called 'strawberry' appearance, especially in the fornices. Secondary redness and œdema of the labia and dermatitis of the perivulvar skin and inner aspects of thighs are usually present. The urethral orifice is red and pouting, and is sometimes infected. The endocervix and the bladder are rarely involved. A drop of fresh discharge mixed with a little warm saline examined microscopically reveals many pus cells, squames and a number of trichomonads (fig. 7). The latter is a flagellate protozoon slightly larger than a pus cell, clearly recognizable by its lively motility. Its precise morphology can only be shown in stained specimens and cultures (Kean and Day, 1954).

Treatment must be thorough and sustained. Two pessaries of acetarsol or 'penotrane' should be inserted into the vaginal fornices each night for

four to six weeks. Treatment must be continued during the menses, and a check smear examined immediately after the first period following cessation of treatment. Resistant and recurrent cases are occasionally encountered due to inadequate treatment, reinfection from sites inaccessible to local therapy or from the husband, or to resistant strains of the organism. In the male the infection may be in the prepuce, urethra, prostate, vesicles or bladder—and may be entirely asymptomatic. According to Coutts *et al.* (1955), 58 per cent. of men with infected wives, and 68 per cent. of men

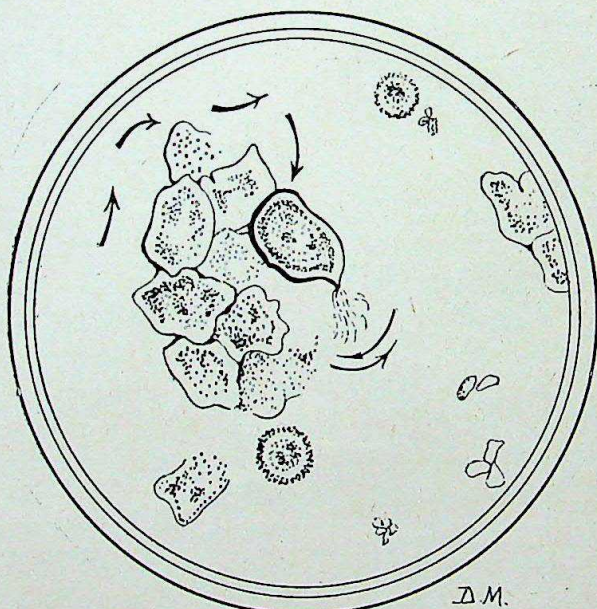


FIG. 7.—Trichomonas infection. Artist's sketch from smear of fresh discharge ($\times 450$), showing many epithelial squames, two pus cells, and one trichomonas. Arrows indicate directions of movements of organism while under observation.

with non-gonococcal urethritis, give positive tests. If the husband is untreated only 35 per cent. of women are cured. A solution of these problems has been sought by systemic treatment of both partners. Acinitrazole ('tritheon'), in the form of 100-mg. oral tablets, is given three times a day for ten days to husband and wife and the course is repeated if required. Some good results have been reported (Plentl *et al.*, 1956), and the method merits further trial.

Acute gonorrhœa in adults takes the form of acute cervicitis, urethritis and Bartholinitis, with occasional upward spread later to the Fallopian tubes, ovaries and pelvic peritoneum. Chronic pelvic infection may result. In children, the infection, usually acquired from infected towels, linen and the like, is an acute vulvo-vaginitis without any tendency to upward spread or

chronicity. Isolation is urgent owing to the danger of spread in the home or school. Both these acute conditions can be readily recognized from stained smears and cultures. When suspected the patients should be referred immediately to an appropriate hospital clinic.



Fig. 8.—*Monilia* infection. Copious thick white material covering the vaginal wall.

Treatment of the acute condition is generally by a single massive dose of penicillin, with careful follow-up by repeated bacteriological examinations. The possibility of simultaneous syphilitic infection is emphasized and checked by Wassermann reactions before and after treatment. Diagnosis of the chronic condition in the adult is more difficult as the organisms tend to be deep seated in the cervical glands, secondary infection is common, and the complement fixation test is unreliable.

Senile vaginitis and endometritis (with occasional associated pyometra) occur in post-menopausal women, due to coccal, coli, or trichomonas infection helped by the lowered local resistance of the tissues in this age-group. The discharge, thick, offensive, and

occasionally blood-stained, tends to come in small gushes. It is associated with a typical thin vaginal wall covered with large scarlet patches, soreness and redness of the introitus and vestibule, and dyspareunia. Ulceration, scarring and stenosis may result.

Treatment.—These post-menopausal cases should be referred to hospital for diagnosis and treatment as the possibility of malignancy must be eliminated. Treatment is usually by small doses of oestrogens in the form of pessaries or ointment.

Foreign bodies, such as pessaries, 'tampax', cotton-wool, abortifacients, contraceptive caps, cause a purulent discharge which soon becomes offensive and later blood-stained. Removal of the foreign body, followed by simple douching with weak hypochlorite solution for a few days rapidly clears the condition.

Monilia infection produces a vulvo-vaginitis associated with marked pruritus and little external discharge. A large red patch covers the vulva and perineum. Speculum examination of the vagina reveals copious thick white material covering the walls completely or in patches (fig. 8). On removal of this discharge the vaginal walls are red and rugose. Stained smears show the typical hyphæ and spores of the fungus (fig. 9), which

flourishes in the presence of glycogen and is therefore usually associated with pregnancy or glycosuria.

Treatment.—The vulva and vagina must be thoroughly cleansed with swabs soaked in sodium bicarbonate, dried and painted with 2 per cent. gentian violet daily for a fortnight, then once a week for a further two to four weeks. With careful technique, using a minimal amount of the dye, the treatment does not stain the underclothes or depress the patient (Donald, 1956). Recurrence, especially during pregnancy, may be due to the rugose

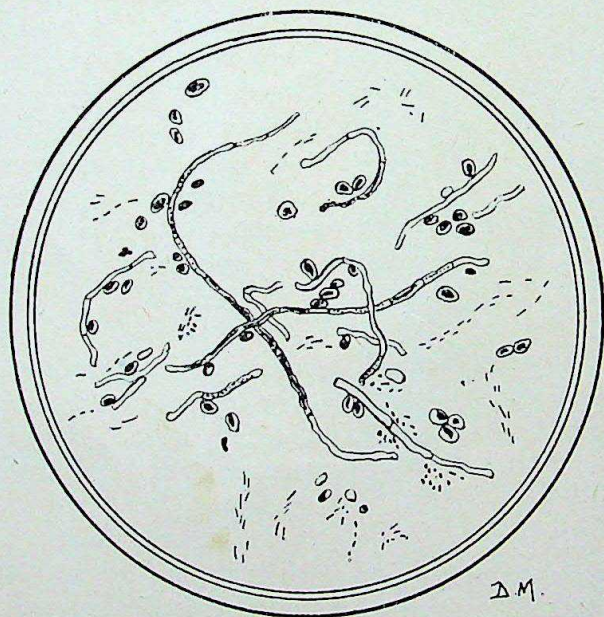


FIG. 9.—Monilia infection. Artist's sketch from stained smear of discharge ($\times 400$), showing hyphae and spores.

vaginal skin or reinfection from the bowel. A single vulval and vaginal painting with a weak tincture of iodine under anæsthesia should then be tried. Nystatin, in the form of pessaries and oral tablets, is on trial. Stewart (1956) and Childs (1956) have given accounts of its use in oral thrush and pulmonary moniliasis, and Donald (1956) quotes a personal communication from Barr who reports encouraging results, using the vaginal pessaries, in his Glasgow unit. It may prove a useful addition to present methods.

WATERY, SEROUS OR BLOOD-STAINED DISCHARGES

These must always be investigated in hospital as they are so often evidence of malignancy. They may occasionally be due to erosion, polypi, fibroids or foreign bodies.

OFFENSIVE DISCHARGES

The significance of offensiveness as an objective sign is considerable, as it

is a prominent feature of necrotic malignant neoplasms of the cervix, the vagina, and occasionally the vulva. Other possible causes to be kept in mind are infected retained products of conception, foreign bodies, a sloughing fibroid polypus, pyometra, and urinary and fæcal fistulæ.

GENERAL INSTRUCTIONS

A patient under treatment for vaginal discharge should maintain careful vulval toilet, avoid coitus, and refrain from douches unless specifically instructed.

A woman's anxieties must be patiently allayed as they so commonly lead to overtreatment.

Many of these patients may be successfully treated in domiciliary practice, provided always that full and careful examination has been carried out. In the interests of safety, however, the following conditions should be referred to hospital:—

- (1) Pre-pubertal, menopausal and post-menopausal cases.
- (2) Blood-stained or serous discharges, particularly those following coitus or vaginal examination.
- (3) All but the simplest erosions.
- (4) Cases not responding to treatment or suffering recurrences.
- (5) Suspected gonococcal cases.
- (6) Offensive discharges other than those due to simple foreign bodies.

I would record my grateful thanks to the Department of Photography, The Medical School, University of Durham, for the illustrations, and particularly to Miss Mustart of that department for the sketches.

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GYNÆCOLOGICAL PROBLEMS OF ADOLESCENCE

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ADOLESCENCE represents the transition from childhood to maturity and the beginning of the reproductive period and is a period of great physical and mental readjustment. In the majority of girls this is achieved with no more than minor disturbances and the gynæcological problems encountered take the form mainly of functional disorders; tumours are rare and major infections uncommon.

The physical changes of puberty begin to make their appearance by the age of nine or ten and precede the onset of menstruation by several years. The breasts develop, hair appears on the pubes and in the axillæ, the uterus and vagina and the labia minora reach their adult size and the bodily configuration changes with the laying down of varying amounts of fat. There is often instability of the vasomotor system which may lead to pallor, a tendency to blushing, tachycardia and irregularities in cardiac rhythm. Psychological manifestations may take the form of shyness, excitability, insomnia, moodiness and irritability. There is a tendency to defy authority as many parents find in their dealings with adolescent daughters. Certain general disorders may make their appearance at this time: these include epilepsy, migraine and asthma, whilst skin diseases, especially acne, are common. These disturbing symptoms are often transient and disappear when full maturity is achieved.

EXAMINATION OF THE ADOLESCENT GIRL

When there is a gynæcological problem the girl is usually accompanied by her mother or some other female relation. It is desirable, whenever possible, to interview the girl alone. She will talk more freely and it is possible to elicit not only the main symptoms but the girl's own feelings concerning them. The mother should also be seen alone and will often present a different viewpoint; mothers often exaggerate their daughters' troubles and have to be persuaded to adopt a more helpful attitude.

A general examination is important and useful in gaining the girl's confidence. Height, weight and general bodily configuration should be noted, also skin texture and any tendency to acne or seborrhœa. The distribution of hair and the secondary sex characters are important in relation to the problem as a whole. Pelvic examination will necessarily be restricted to rectal examination, though the hymen should be inspected in cases of amenorrhœa, to make sure that it is perforate. A satisfactory bimanual

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examination can be made per rectum, at least to ascertain the size and position of the uterus and to exclude any pelvic tumour. If vaginal examination is indicated, as in certain cases of amenorrhœa and of vaginal discharge, it will be carried out under anæsthesia.

THE HYGIENE OF MENSTRUATION

Many of the minor disabilities associated with the menstrual function can be prevented by a sensible outlook on the situation on the part of the girl and her mother and by a proper attention to hygienic needs at the time of the periods. Girls should be informed about menstruation before reaching the age of eleven; the mother is the right person to give the necessary information but where there is no mother or she is unable to talk freely to her daughters, some other person may have to undertake the task. The family doctor can often help by overcoming erroneous and superstitious beliefs. Stress should be laid on menstruation as a normal function and not an illness. A mother often has to be persuaded that it is good for a girl to have a daily bath during menstruation, to wash carefully and use talcum powder liberally. Emphasis should be placed upon the need for adequate exercise and the mother should ensure that her daughter has adequate facilities, whether at school or at work, for changing soiled sanitary towels. Schools are often found to be seriously at fault in this respect and thus adolescent girls suffer much unnecessary discomfort.

PRECOCIOUS PUBERTY

Precocious puberty may be defined as the appearance of secondary sex characters or of menstruation before the age of eight years. In most cases it is due to premature development of the anterior pituitary with secretion of gonadotrophins. In these cases large cystic ovaries may be found. Lesions of the hypothalamus are rarer; they take the form of tumours, cysts, hydrocephalus or encephalitis. Granulosa cell tumour of the ovary, rare in young children, also causes precocious puberty, often with severe uterine bleeding. Hyperplasia or tumours of the adrenal cortex have a virilizing effect in girls.

Investigation of precocious puberty consists in careful examination of the abdomen, if necessary under anæsthesia and combined with rectal examination to exclude a pelvic tumour. If a granulosa cell tumour is present it should be removed immediately as it is potentially malignant. The majority of cases will prove to be functional and require no special treatment. It is wise to warn the parents of the risk of pregnancy.

PRIMARY AMENORRHŒA

Amenorrhœa in adolescent girls may be primary or secondary. Primary amenorrhœa may be said to exist when menstruation has not begun by the age of seventeen. It must be distinguished from cryptomenorrhœa where the menstrual flow is obstructed by an imperforate hymen.

The onset of menstruation may be delayed for physiological reasons. The girl is of normal appearance and well developed but normal menstruation may not be established before the age of eighteen or even later. It then continues normally and fertility is also normal.

The mechanism of normal menstruation is complex and depends upon the proper functioning of several organs. These include at least the hypothalamus, the anterior pituitary, the thyroid, the adrenal cortex, the ovaries and the uterus. Failure of function or faulty development of any of these may lead to amenorrhœa. Gross endocrine disorder is manifest in the girl's general appearance. Anterior pituitary disorder is shown by obesity, excessive thinness or lack of secondary sex characters. Adrenal virilism is uncommon in adolescents but might be suspected in a masculine, excessively hirsute girl; 17-ketosteroids are present in the urine in excessive amounts in this condition.

When menstruation has not appeared before the age of seventeen, it is reasonable for advice to be sought. A general examination is first carried out with reference to obesity or excessive thinness, stigmata of endocrine abnormality and the development of secondary sex characters. Vaginal examination will not be performed but the orifice of the vagina is inspected to exclude an imperforate hymen with cryptomenorrhœa. A vaginal smear can be taken with little disturbance and gives a useful indication of the œstrogen secretion of the ovaries. A rectal examination, gently performed, gives a good impression of the size and position of the uterus and will also exclude a pelvic tumour.

If a congenital malformation of the pelvic organs is suspected, an examination should be carried out under anæsthesia. Cryptomenorrhœa is dealt with by incision of the imperforate hymen; stringent precautions against infection are essential and the retained menstuum may be gently expressed by suprapubic pressure and left to drain spontaneously. Cases of congenital absence of the vagina and uterus, though rare, are occasionally encountered; no immediate treatment is required here unless the girl wishes to marry, when a plastic operation may be undertaken to create an artificial vagina. This will permit normal intercourse, though the possibility of childbearing does not exist.

In healthy girls in whom the onset of menstruation is delayed for no apparent reason it is often desirable to attempt to establish it by means of hormone treatment. The ovarian hormones offer the best chance of success. It is regrettable that the use of pituitary gonadotrophins, in theory ideal for this purpose, should prove disappointing in practice. Production of artificial cycles by means of œstrogens and progestogens is often brilliantly successful, spontaneous cycles continuing after cessation of treatment.

The principle of treatment, which is based on the method described by Hamblen, is to give first œstrogens to 'prime' the uterus and produce withdrawal bleeding. Later, a progestogen is added; the convenient oral progestogen, ethisterone (pregneninolone; ethinyltestosterone), is the best in

practice. In deciding on the œstrogen to be used it must be remembered that 1 mg. of stilbœstrol given twice a day for fourteen days and then withdrawn will produce uterine bleeding if the uterus is capable of responding to œstrogens. In practice, treatment is continued for twenty-one days in imitation of the normal ovarian cycle. Unfortunately, stilbœstrol tends to cause nausea and vomiting in adolescent girls; ethinylœstradiol is usually better tolerated. The equivalent dose of the latter is 0.05 mg. twice a day.

A scheme of treatment which has been found to succeed in many cases is as follows. Ethinylœstradiol, 0.05 mg., is given sublingually twice a day for twenty-one days. After a week's rest, during which there may be withdrawal bleeding, this is repeated for a further twenty-one days and again for a third cycle. In the fourth cycle, ethinylœstradiol is given as before, but for the last ten days of treatment, ethisterone, 20 mg. a day, is added. In the fifth cycle, the dose of ethinylœstradiol is halved (this is simply done by breaking the tablets) and that of ethisterone is increased to 30 mg. daily. In the sixth cycle the dose of ethinylœstradiol is halved again and the dose of ethisterone further increased to 40 mg. daily. If treatment is successful withdrawal bleeding will occur and, after treatment is stopped, regular spontaneous menstruation will begin.

If this treatment fails to produce withdrawal bleeding it is likely that there is a degree of underdevelopment of the uterus; further treatment is not likely to succeed although it may be worth repeating the first three cycles with double the dose of œstrogen and completing the treatment if there is a response. In cases which respond to artificial hormone treatment but relapse into amenorrhœa when treatment is stopped, it is likely that there is a fault in the ovaries or anterior pituitary. A second course of treatment is occasionally followed by spontaneous menstruation. It must be admitted, however, that the prognosis in cases of serious underdevelopment of the uterus or ovaries is not good. Fortunately, such cases are uncommon.

SECONDARY AMENORRHŒA

Secondary amenorrhœa is a common symptom in young women; the possibility of pregnancy must not be overlooked. Debilitating diseases, especially in the early stages of pulmonary tuberculosis, may be associated with amenorrhœa. Anorexia nervosa is another disease which may present as amenorrhœa. The onset is often insidious, the periods ceasing before actual loss of weight is apparent and the girl may succeed in concealing for some time the fact that she is not eating. 'Environmental amenorrhœa' is common among girls leaving home to take up institutional life; this applies to nurses in training, students and girls entering the Services. The 'pituitary shock' syndrome is an allied condition where amenorrhœa follows a profound shock. This may be associated with excessive eating and obesity.

In dealing with secondary amenorrhœa, pregnancy, serious organic disease and endocrine disorder must first be excluded. An x-ray of the chest is advisable in all cases and also an estimation of hæmoglobin since some of

these girls are anæmic. If no organic cause is apparent it may be concluded that the amenorrhœa is of environmental origin. In most of these cases spontaneous recovery, with the reappearance of normal menstruation, occurs within six months so that it is unnecessary to give immediate treatment, except on general lines. If menstruation fails to reappear after six months it is reasonable to give hormone treatment, as for primary amenorrhœa.

DYSMENORRHŒA

In the adolescent girl dysmenorrhœa is invariably of the primary, intrinsic or spasmodic type. Its clinical features are well known. The pain, which may be very severe, tends to coincide with the onset of menstruation. It is felt in the lower abdomen and pelvis and may be referred to the back or down the legs. It may be accompanied by nausea, vomiting and fainting. Usually it lasts no more than a few hours but it may be prolonged for a day or more.

The exact nature of the pain of spasmodic dysmenorrhœa is uncertain but it appears to be associated with the powerful uterine contractions which occur during the first day or two of menstruation. It is present only in post-ovulatory menstruation, anovular bleeding being painless. Hence the onset of menstruation and its first year or two may be characterized by painless, often irregular, bleeding, dysmenorrhœa appearing later. The natural history of dysmenorrhœa is interesting; it affects mainly young women and tends to disappear after the age of thirty. Marriage often leads to improvement and childbearing to a complete cure. If ischæmia of the uterus causes pain, then it might be expected that the relative increase in fibrous tissue and the loss of muscular power which occurs after childbearing and as the uterus ages, are responsible for recovery from spasmodic dysmenorrhœa. This is probably an over-simplification of the problem.

Further evidence on spasmodic dysmenorrhœa has been obtained by experimental work which has shown that sufferers from dysmenorrhœa have a lower threshold for pain than other women and than men; this fact is probably the most important in the causation of the condition.

Spasmodic dysmenorrhœa is an important socio-economic disease. Many girls are referred for treatment because they have acquired the habit of staying away from work or from school for the first day or two of menstruation. The condition tends to affect mainly girls of sedentary habits and is uncommon among girls working out of doors and performing manual labour.

The treatment of spasmodic dysmenorrhœa depends upon its severity and the degree of disability it causes. At the outset, it is most important to emphasize to the girl and to her mother that this is a functional condition, that it does not indicate pelvic disease and that recovery can be expected in time. Here it may be noted that retroversion of the uterus, if found in a girl with dysmenorrhœa, is certainly a coincidental finding and of congenital origin. The pain is unlikely to be relieved by correction of the retroversion. In all cases, careful inquiry must be made into the girl's mode

of life and she should be urged to take regular exercise, if possible in the fresh air. Gymnastics, tennis, riding, swimming and all outdoor games are helpful. In addition, remedial exercises should be performed regularly at home. Constipation should be avoided. For the milder cases simple analgesics suffice and should always be tried first. Aspirin alone, or in combination with other drugs, is the analgesic of choice. A combination of aspirin, phenacetin and amphetamine, known under the proprietary name of 'edrisal', is useful, but should not be taken in the evening. Application of heat, either as a hot-water bottle or a hot bath, will help a short attack of severe pain. On no account should alcohol or habit-forming drugs be given.

A simple regime of adequate exercise, attention to hygiene, reassurance and analgesics should be tried initially in every case, further treatment being necessary only when these measures do not succeed. Good results are obtained in many cases by giving oestrogens throughout the cycle, except during menstruation. It has been suggested that this acts by temporarily inhibiting ovulation and producing painless anovulatory bleeding, but I have seen pregnancy occur during such treatment, which has led to doubt on this point. It may be that the oestrogen acts on the uterine blood vessels improving the flow through them and thus relieving ischaemic pain. Treatment consists in the administration of stilboestrol, 1 mg. twice daily, or ethinylœstradiol, 0.05 mg. twice daily, for twenty-one days, beginning on the fifth day of the cycle. Treatment is continued for three cycles and then discontinued. A further course of three cycles may be given if pain recurs on stopping treatment. In many cases six months' treatment gives permanent relief.

Dilatation of the cervix relieves or improves forty to fifty per cent. of cases of spasmodic dysmenorrhœa. In some the pain is temporarily relieved, only to recur after a few months. In these a second dilatation often gives permanent relief. Pelvic sympathectomy is reserved for those cases in which dysmenorrhœa proves intractable. This is rarely found to be necessary in practice, certainly in young girls, although it might be undertaken for incapacitating dysmenorrhœa in an older woman.

PUBERTY MENORRHAGIA

Menstruation is often irregular at its beginning, a year or two elapsing before the adult rhythm is established. In a few cases this irregularity takes the form of very frequent periods or of prolonged episodes of bleeding. In a very few, prolonged heavy uterine bleeding occurs, leading to anæmia and ill health. These cases are referred to as puberty menorrhagia. Abnormal physical signs are rarely found, although biopsy of the endometrium reveals a hyperplasia of metropathic type.

Treatment in milder cases, in which the periods are fairly regular but heavy, consists initially in measures to improve the general health, treatment of anæmia if present and administration of calcium. More severe cases require hormone treatment and here the oestrogens can usefully be used as

uterine hæmostatics. Treatment is begun with ethinylœstradiol, 0.05 mg. sublingually twice daily. This is continued for twenty-one days, unless bleeding occurs during treatment, in which case it is discontinued for an interval of five days and then given again in double the dose. Treatment is continued until the bleeding is controlled, though a further increase in dosage may be necessary before this is achieved. The aim is to produce three withdrawal bleedings at intervals of about twenty-eight days. The dosage of œstrogen is then reduced and ethisterone added in increasing doses as in the treatment of primary amenorrhœa. Normal menstruation may be expected after six months of successful treatment.

This method is somewhat tedious but is so successful that, with perseverance, curettage is rarely if ever necessary and once the initial bleeding has been controlled it is a simple matter to bring about normal cycles.

VAGINAL DISCHARGE

Vaginal discharge is a comparatively common symptom in adolescent girls and in general presents much the same problems as does leucorrhœa in the adult woman. The causes may be divided into two main groups: true leucorrhœa, representing an excess of normal vaginal secretion, and pathological vaginal discharge. It is quite common for young girls to have a thick, curdy vaginal discharge. This can be simply investigated by taking a vaginal swab. The swab reveals a strongly acid discharge which contains only desquamated vaginal cells and Döderlein's bacilli. This excess of secretion is contributed to by constipation, over-exertion and nervous factors. It causes no other symptoms and when recognized is best treated by reassurance and simple advice on general hygiene.

Pathological discharges in adolescents may be caused by cervical erosion, trichomonas vaginitis and vaginal thrush. A foreign body in the vagina is another possible cause though less common than in younger children. Full investigation is rarely possible without examination under anæsthesia. A very small speculum is passed so that minimal damage is caused. The cervix and vaginal walls are inspected, thus excluding a foreign body or a congenital erosion of the cervix. A swab is taken from the discharge for laboratory examination, including culture. Many cases will be found to be due to congenital erosion of the cervix, often with secondary infection. These are treated by electrocauterization. Infections of the vagina are treated along the same lines as those in adult women; such treatment is often best given in hospital.

CONCLUSION

The adolescent girl with a gynæcological problem needs careful and tactful handling. Some of these problems arise from ignorance and faulty hygiene, others represent conditions causing serious disability which are, however, amenable to treatment. The future of the girl as an adult woman will depend very much upon how her case is handled at this difficult and testing time in her life.

THE FEMALE CONTRIBUTION TO THE STERILE MARRIAGE

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WHEN considering the role of the woman in the sterile marriage the practitioner must never forget that sub-fertility factors are usually found in both partners, and both the man and the woman must be investigated. It is the purpose of this article, however, to consider the woman's responsibility only, excluding those factors which give rise to absolute sterility and for which, as a rule, little can be done.

In the case of the apparently normal woman who consults her doctor because she has failed to conceive, one, or a combination, of four conditions will be found and, as a rule, it is a simple matter to investigate and elucidate the cause of her difficulty. These four conditions are:—

- (1) Failure to ovulate or defective ovulation.
- (2) Failure to elaborate a satisfactory oestrogenic cervical mucus at the time of ovulation.
- (3) Failure to prepare the endometrium satisfactorily for the nidation of the fertilized ovum, or disease of the endometrium such as tuberculosis.
- (4) Obstruction of one or both tubes.

Although these four factors must be considered separately, a combination of faults is commonly found.

FAILURE TO OVULATE OR DEFECTIVE OVULATION

A woman usually ovulates about fifteen days before the anticipated onset of a period. This means that, in a woman who menstruates every 28 days, ovulation will take place on the 13th day from the first day of the last period; in a woman with a 21-day cycle, ovulation will take place on the 6th day from the first day of the last period. It is important to assess this day because timing of intercourse relative to this day is most important as it is highly probable that the ovum, once extruded from the ovary, will not survive for longer than about twelve hours unless it is fertilized. Intercourse must therefore take place in anticipation of the day of ovulation and not in arrears. If this view is correct, fertilization depends more upon the ability of the spermatozoa to survive inside the female passages for two or three days than upon the capacity of the ovum to await fertilization. Timing is thus very important and at the first consultation this can be explained and the woman's fertile days calculated mathematically while awaiting a more accurate assessment.

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METHOD OF ASSESSING THE DATE OF OVULATION

Basal body temperature.—The body temperature changes throughout the menstrual cycle. A normally ovulating woman has a diphasic temperature. If the early morning temperature be recorded, preferably by inserting the thermometer into the rectum or into the vagina, this diphasic character will be apparent. Men, women past the menopause, and children do not exhibit this cyclical fluctuation, which is considered to be due to a depression of the metabolism-stimulating hormone of the anterior pituitary gland by œstrone and a stimulation of it by progesterone. Thus, the pattern of the temperature chart is diphasic, with the temperature fluctuating around a low mean before ovulation and fluctuating around a higher mean after ovulation when the corpus luteum is elaborating progesterone. Such a temperature chart is of more value to the medical adviser than to the patient, since the rise in temperature follows upon the activity of the corpus luteum and by the time it occurs the ovum, if unfertilized, is already dead. Here it must be emphasized once more that intercourse is likely to be most fertile when undertaken immediately before or at the time of temperature change, but not afterwards.

Cervical mucus.—Although this method of assessment is a simple procedure it cannot be relied upon absolutely and is most useful when used in conjunction with inspection of the cervix to assess the character of the cervical mucus, because in health there is a cyclical change in the character of the cervical secretion throughout the menstrual cycle. If the cervix of a normally menstruating woman be exposed at the time of ovulation mucus can be seen to be streaming out from the cervical canal and clinging to the posterior lip of the cervix. This mucus is clear and glycerin-like in character and can easily be sucked out with a suction syringe or lifted out with a pair of artery forceps. Certain physical characteristics can then be noted, the chief of which is the fibrosity of the mucus: i.e. the capacity of the mucus to be stretched into threads of 6 to 10 cm. long. This can be done by separating the blades of the forceps holding the mucus. If fibrosity is satisfactory the mucus will stretch between the two open blades as a thin elastic thread.

After ovulation, this mucus changes its character, it generally becomes more and more 'tacky' until finally, before menstruation it is thick, 'tacky' and opaque. 'Tackiness' is assessed by placing a blob on a microscope slide, compressing it with another slide and then separating them when this mucus, unlike the mucus at the time of ovulation, will adhere to the one and break away from the other. The thin elastic mucus seen at the time of ovulation is sometimes called 'ovulatory' mucus; this is an unsatisfactory term and the mucus would be more accurately described as œstrogenic mucus since it is secreted by the cervical glands when they are acting under the stimulus of œstrone only; the 'tacky' mucus is secreted by the glands when they are acting under the influence of œstrone plus progesterone. Thus, it is the change from one kind of mucus to the other which acts as an indicator that ovulation has taken place, and that a corpus luteum has been formed.

Women who menstruate without ovulating do not show this change but

the mucus remains clear, fibrotic (elastic) and glycerin-like throughout the cycle. Likewise, a woman who has missed a period by about a fortnight will have an opaque 'tacky' mucus if the delay is due to pregnancy, but if the delay is due to an unruptured Graafian follicle, as is seen in the case of metropathia hæmorrhagica, the mucus will be fibrotic. This mucus is immiscible with semen, and when they are in contact they behave as two colloids and a physical interface is formed which offers obstruction to the passage of certain spermatozoa while allowing others to pass through easily. The behaviour of the spermatozoa can be observed if semen and cervical mucus be placed in contact on a slide and examined microscopically.

The spermatozoa on the semen side soon collect in a dense mass up against the interface and they are orientated with the heads facing the mucus, but the majority, despite vigorous movements, fail to pass the interface whilst others penetrate the mucus with some effort. There are yet others which appear to overcome the resistance of the mucus with ease. Only the vigorous and favourably shaped spermatozoa are capable of doing this.

The fact of ovulation is also assessed by subjecting to microscopy the endometrium, removed a few days before menstruation.

Apart from the normal secretions of the cervix certain pathological states may be found.

(1) The cervix may be dry and devoid of mucus during the presumed ovulatory phase. This is seen in women who fail to produce Graafian follicles or who produce them at irregular intervals. They often exhibit android characteristics or suffer from obesity of the pituitary type and menstruate irregularly. Spermatozoa appear to be unable to invade this type of cervix.

(2) There may be a thick, opaque, gelatinous, non-fibrotic mucus, containing microscopically large numbers of leucocytes; this type of mucus is associated with chronic cervicitis. Spermatozoa appear to become enmeshed in such a mucus.

(3) There may be a frank purulent discharge from acute inflammation of the cervix.

It is at this stage that a word of warning is necessary since it is assumed that anyone investigating a sterile marriage will have had the semen tested by an expert and the report may have been 'normally fertile'. The real question to be answered is whether the semen is capable of fertilizing the woman against whom it is matched. A semen may be capable of fertilizing a young woman of 20 years with excellent oestrogenic mucus, but incapable of fertilizing a woman of, say, 35 years, less equipped for the purpose, since there are degrees in the quality of the mucus of almost infinite variety.

The final test of this mucus therefore must be its capacity to permit penetration by, and to support the life of, the spermatozoa against which it is matched and this capacity is elucidated by the post-coital test.

THE POST-COITAL TEST

This test is the most important test of all. It is simple to perform and its

results are most instructive because, until a dense active population of motile spermatozoa is found in an adequate oestrogenic mucus within the cervix after intercourse, conception is not likely to take place.

The woman is asked to report on, or about, her fertile days and within a period of seven to twelve hours of intercourse having taken place. It is also wise to instruct the partners to abstain from intercourse for three or four days beforehand. The cervix is exposed with a bivalve speculum and the mucus in the cervical canal removed with a suction syringe. The mucus is then examined, its naked-eye appearance being noted, and it is also examined under the microscope. Any increase in viscosity is likely to be unfavourable for the migration of spermatozoa. Under the microscope a dense population of motile spermatozoa should be found. Four or five progressive spermatozoa should be seen per high-power field; anything less than this calls for an explanation.

A poor post-coital test implies one of three faults: (1) the semen is inadequate; (2) the cervical mucus is unsatisfactory; (3) there is a fault in coital mechanics.

Faulty mechanics.—There can be little doubt that certain mechanical conditions exist which prevent satisfactory insemination. The observer will be led to the conclusion if, in spite of a satisfactory semen test, satisfactory cervical mucus, and no fault in potency, a post-coital test fails to demonstrate an adequate quantity of spermatozoa in the cervical canal. A retroverted uterus is a common cause of failure of insemination since in this instance the external os may be directed away from the seminal ejaculate which may be deposited and 'lost' in the posterior fornix.

Other mechanical factors are not so obvious but a narrow vagina associated with an android pelvis sometimes prevents deep penetration and therefore the semen is lost in the vagina and spermatozoa cannot reach the os as they are destroyed by acid vaginal secretion; it is in such cases that a pre-coital alkaline douche is useful. A small or pin-hole os, presenting, as it does, a very small area for semen-mucus contact, may fail to allow the passage of an adequate number of spermatozoa from a semen of unsatisfactory density.

Of recent years, it has become the practice of seminologists to be satisfied with a post-coital test alone but, since the cervical mucus filters the good from the bad, a post-coital test can only indicate the presence of an adequate number of satisfactory spermatozoa. It cannot give the differential count of normal and abnormal sperms which is so valuable in assessing the quality of the male. Therefore, valuable as it is, the post-coital test should be used as an adjunct to, and not as a substitute for, a semen test.

Before leaving the subject of the cervical mucus it is of interest to note its relevance to the reason why the simple, time-honoured operation of dilating the cervix satisfied our forebears and many of us at the present time. It may be that dilatation will increase the area of semen-mucus contact and thus allow a larger number of spermatozoa the opportunity of migrating into

the cervical fluid. Thus, in this way, i.e. by dilating the cervix, one may compensate for a semen of poor density.

FAILURE TO PREPARE THE ENDOMETRIUM SATISFACTORILY FOR THE NIDATION OF A FERTILIZED EGG

Fertility implies not only that conception should take place but that the fertilized egg should be capable of embedding in the endometrium, and the endometrium should be adequately prepared to receive and support its life. The preparation is the result of the synergistic action of the two hormones, œstrone and progesterone, elaborated by the corpus luteum. There can be little doubt that there are varying degrees of endometrial preparation, and all operators can verify at laparotomy that corpora lutea vary in size in different individuals at the same time in the cycle. Some women develop a large corpus luteum when the endometrium is adequately prepared. In others, the corpus luteum is less well-developed and presumably the endometrium less satisfactorily prepared. An extended experience of endometrial biopsies, taken in the luteal phase, will lead the microscopist to recognize a good and a poor preparation.

Thus, an endometrial biopsy, taken a few days before the anticipated onset of a period will, on the one hand, confirm ovulation, and, on the other hand, give an idea of the amount of hormones elaborated by the corpus luteum. Variations in the microscopic picture of the endometrium may be due to variations in the qualities of the luteal hormones, or variations in the endometrial response to these hormones, as Bourne suggests. Whatever may be the explanation, the fact remains that many sub-fertile women conceive by the simple plan of having intercourse on their fertile days and follow this by taking small quantities of luteal hormones during the premenstrual phase.

A common plan is to suggest intercourse (in a woman with a 28-day cycle) on days 12, 13 and 14 of her cycle; that is to say, on days 12, 13 and 14 from the first day of the period, counting the first day inclusively, and from day 12 she should take one 0.3-mg. tablet of dienœstrol and one 5-mg. 'linguet' of ethisterone daily, and continue taking these tablets until either a period begins, when they should be discontinued, or, if pregnancy ensues, until the 18th week of the pregnancy. In the latter instance, she is advised to continue for 18 weeks because if this plan works it implies that endometrial preparation was at fault and, if she discontinues the hormones, the environment of the growing embryo will become adverse, it will die and be discarded in miscarriage. After the eighteenth week the placenta will be fully developed and will have taken over the control of the hormone production. An endometrial biopsy will also permit the endometrium to be scrutinized generally, with particular reference to giant cell formation as seen in pelvic tuberculosis. The incidence of giant cells in the endometrium varies considerably from one part of the country to another. Many report the incidence in sterile women to be as high as 5 per cent.; their presence appears to be an absolute bar to fertility.

PATENCY OF THE TUBES

Tubal factors.—Tubal factors as a cause of sterility would appear to be of major importance and observers report that in about 50 per cent. of cases a tubal factor is present. Most of these abnormalities of the tubes, such as developmental failure, constrictions, tubal spasms, mucus occlusion and frank inflammation, tuberculous or otherwise, cannot be detected by history or physical examination alone; in fact, a tube palpable at the time of physical examination is often found to be open, whereas in patients with occluded tubes the tubes sometimes on palpation appear to be normal.

There are two methods in general use to determine tubal patency:—

- (1) Utero-tubal insufflation. (2) Hysterosalpingography.

Utero-tubal insufflation is a simple procedure, and, provided that proper precautions are taken, it is perfectly safe. The major precaution is always to use carbon dioxide as the gas, since, if by chance it should enter the blood stream, its absorption is rapid and any effects from the procedure are of shorter duration than when air or oxygen is used. Air should be condemned because of its large nitrogen content which is practically non-absorbable. Several fatalities have been recorded from embolus but in most cases the gas used has been other than carbon dioxide. Of equal importance is an appreciation of the contraindications: (1) Chronic purulent cervicitis. (2) Any acute or recently acute pelvic inflammation. (3) Irregular menstrual bleeding.

Provided these elementary precautions are observed the procedure is safe, and gives most useful information, since not only can tubal patency be demonstrated but, if a kymograph is attached to the machine used, definite cyclical fluctuation of the pressure of the gas can be demonstrated due apparently to tubal peristalsis. These rhythmic contractions are only present in healthy tubes and are most frequent and show the largest range, at, or about, the time of ovulation when the tubes are acting under the influence of œstrin. These peristaltic waves presumably occur spontaneously about the mid-interval of the menstrual cycle; i.e. at the time of ovulation and, acting together with the cilia of the tubal mucous membrane, are responsible for a flow of fluid down the tubes to the uterus. This guides the spermatozoa up the tube, since these swim against the current. At the same time the immotile fertilized ovum, expelled directly into the ostium of the tube, becomes enmeshed in this fluid and is carried down to the uterus where embedding takes place.

This mechanism is beautifully timed; starting as it does, a few days before ovulation, and reaching its height about this time, it serves to guide the spermatozoa upwards and then finally to deliver the fertilized ovum into the uterus. About five days after the rupture of the Graafian follicle the corpus luteum is fully developed and is elaborating progesterone, and the synergistic action of progesterone and œstrin appears to render the tubes and the uterus quiescent. It is just about then, i.e. four or five days after ovulation, that the fertilized ovum is assumed, judging by analogy with the lower animals, to reach the then quiescent uterus where nidation takes place.

While meditating on this remarkable timing, it is interesting to speculate on the disasters which might follow a hitch. Too rapid movements of the tubes might result in nidation taking place low in the uterus, giving rise to placenta prævia; a delay might allow the fertilized egg to be sufficiently developed to nidate in one of the tubes, resulting in a tubal pregnancy.

Good as insufflation is in demonstrating patency and also, by reason of these rhythmical fluctuations, the condition of the tubes, it cannot always demonstrate the condition of both tubes, and many believe that a *hysterosalpingogram* is of more use, since here one has visual evidence of the shape and the patency of the tubes. Furthermore, it is recorded in the literature that about 40 per cent. of women who have a satisfactory result from a salpingogram achieve a pregnancy within six months. During insufflation gas is assumed to pass along the tubes because the pressure remains stationary or falls while the gas is flowing and because of the rhythmic changes in pressure as shown by the kymograph. Also, after the insufflation is finished and the patient sits up, she occasionally experiences shoulder pains, presumably due to collection of gas under the diaphragm. More direct evidence is obtained by auscultation over the lower abdomen when the observer can hear the gas passing into the peritoneal cavity. It is not easy to be certain that the gas passes along both tubes. In cases of unilateral obstruction, or where a tube has been removed, gas is still heard to pass but, owing to the fallibility of the conduction of sound, one cannot be quite certain of the side on which the flow is heard.

It might be argued that it is immaterial whether both tubes are open or not, but a brief consideration of the physiological action of the tubes at the time of fertilization will show how important it is to know that both tubes are open or, at least, that the tube is open on the side of the ovulating ovary. At the time of ovulation an egg is extruded from one or other ovary and there is some evidence to indicate that a woman does not ovulate from alternate ovaries but that she does so repeatedly, often for several years, from one ovary, the other being held, as it were, in reserve. Even if she did ovulate first from one and then from the other ovary, at most she would ovulate six times a year from the left ovary and six times from the right, but, even in these circumstances, her chances of conception would be considerably reduced if one tube were obstructed.

Admittedly pregnancies have been recorded in women who have had an ovary and the contralateral tube removed. In these circumstances a pregnancy could only occur if the ovum migrates across the pelvis or if the remaining tube grasped the opposite ovary with its fimbria. Such cases are rare, but being rare, find their way into literature.

It used to be thought that the ovum was expelled forcibly in a projectile fashion from the Graafian follicle. This is now known to be incorrect; the ovum merely oozes out of the Graafian follicle with the liquor folliculi when the follicle ruptures. Furthermore, many ingenious experiments have shown that muscular bands contained within the mesenteries of the uterus, tubes

and ovaries, pull the ampullæ of the tubes down over the corresponding ovaries almost as sacks. The ovaries now rotate on their longitudinal axes so that first the anterior and then the posterior surfaces are exposed to the sweep of the fimbriæ as they move over the surface of the ovaries and as a result the ovum enters its corresponding tube directly.

This account of the physiology of fertilization explains many problems:—

(1) The tubes must possess fimbriæ, be active and not have the cilia of their mucous membrane destroyed by inflammation. Hence the bad results recorded from bilateral salpingostomy following upon bilateral hydrosalpinx because in this instance the surgeon cannot restore the fimbriæ, the whole of the tube is fibrosed and is not likely to exhibit peristaltic movements and the cilia of the mucous membrane of the tube are destroyed.

(2) The fact that operations for obstructions of the tubes at their uterine end give better results than those for obstruction at the ovarian end. Here, as a rule, the fimbriæ are present, the cilia active, and the tube is not fibrosed. The operation merely results in shortening the tubes.

(3) The frequent failure of conception following salpingectomy for ectopic gestation. Here it is obvious that the ovulating ovary is on the side of the ectopic pregnancy and if it is conserved it is likely to continue to ovulate. When operating for an ectopic gestation, provided that the other ovary is present, the ovary on the ectopic side should therefore be removed.

(4) A salpingogram is of more use than a utero-tubal insufflation.

(5) That if the only cause of sterility in a marriage is proved to be unilateral obstruction the patient should be investigated to ascertain from which ovary she is ovulating. This can be assessed by culdoscopy: i.e. by passing a culdoscope through the posterior vaginal fornix and visibly observing which is the ovulating ovary. If the ovulating ovary is on the side of the obstructed tube, it is better to remove that ovary so that the reserve ovary might function rather than attempt to repair a damaged tube.

Thus it would appear that the best method of learning the condition of both tubes is hysterosalpingography. Even if a satisfactory tracing has been obtained once or twice by insufflation and the patient remains sterile in spite of all other factors being satisfactory, unilateral obstruction should be suspected and a hysterosalpingogram should be performed. The same contraindications apply here and there is also the danger, when an oily medium is used, of oil embolus. This can be reduced to a minimum provided the following two precautions are observed. Hysterosalpingography should never be performed in the premenstrual week when there is hyperæmia of both uterus and tubes and the patient must always be screened at the time the oil is injected. A skilled radiologist can guide the operator and can see immediately if the opaque medium is leaving the genital path. Should this happen the injection should be discontinued at once.

NEUROLOGICAL COMPLICATIONS OF THE ACUTE SPECIFIC FEVERS

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NEUROLOGICAL complications of the acute infectious fevers are rare: even measles encephalitis, probably the most familiar example, occurs only once in a thousand cases of the exanthema. These illnesses, however, are for the most part dramatic and alarming, and unless the physician is aware of their existence they may lead not only to diagnostic confusion, but also to injudicious or even harmful therapeutic interference. Descriptions of case-material recorded over the past century yield useful generalizations to guide the practitioner in diagnosis and management.

MEASLES, VARICELLA, AND RUBELLA

The neurological complications of measles, chickenpox, and rubella are identical in type and vary only in detail. They arise on the common basis of a widespread inflammatory lesion, disseminated throughout the white matter of the nervous system, characterized by cellular infiltration and patchy demyelination concentrated in the region surrounding the cerebral blood vessels, and particularly the small veins—a perivenous demyelinating encephalomyelitis. Not only are identical lesions found following each of these three diseases, but they are also quite indistinguishable from the findings occasionally encountered after banal infections, and after vaccination against smallpox and various other sterile inoculations. In all probability therefore they are manifestations of a non-specific allergic reaction to a variety of antigens and not directly due to virus invasion. On this pathological basis arises a triad of clinical syndromes: *encephalitis*, *myelitis*, and *polyneuritis*, or more accurately (since this form of polyneuritis appears to have its origin in lesions involving the spinal roots) *polyradiculitis*. Mixed and transitional syndromes are often encountered. Quite often, for example, a partial transverse lesion of the spinal cord, or focal muscular wasting of root origin, complicates a predominantly encephalitic illness. In the same way transient disturbance of consciousness, or meningism, may occur in a case of transverse or ascending myelitis, or in a patient with severe polyradiculitis. Ninety per cent. of cases, however, are predominantly encephalitic, with or without evidence of simultaneous involvement of cord or nerve roots. The remaining ten per cent. comprise instances of myelitis or polyradiculitis in which encephalitic symptoms are absent or, at the most, quite evanescent.

In each of these three instances it is the older patients who are most liable to develop neurological complications, and since rubella tends to

occur later in childhood and adolescence than the other two, the age distribution of neurological complications in this exanthema is the highest of the three, no less than one-third of such cases occurring after the age of sixteen. Furthermore, it should be noted that these neurological disorders are far from being complications of severe exanthemata. Their occurrence is indeed independent of the severity of the initiating infectious disease, and measles encephalitis has several times been reported after the mild illness which follows the use of attenuating doses of gamma globulin. Thirdly, although the spinal fluid in cases of polyradiculitis (the condition otherwise familiar as infective polyneuritis, or Guillain-Barré syndrome) nearly always shows the customary massive increase in protein content, the findings in encephalitis and myelitis are non-specific. The fluid may be normal, but more commonly shows a moderate to marked lymphocytic pleocytosis; this, however, bears no apparent relation to severity, prognosis, or the occurrence of clinical meningism.

ENCEPHALITIS

In a few instances the onset of para-infectious encephalomyelitis precedes the appearance of the rash, and the nature of the neurological disorder becomes clear only after a few days. Most often, however, the various encephalitic illnesses (which have the shortest latent periods) begin as the rash is fading: typically three to four days after its appearance in the case of rubella, four to five in patients with measles, and six to seven in varicella. Polyradiculitis has an average latent period almost twice as long as encephalomyelitis (eight, nine, and eleven to twelve days respectively), myelitis occupying an intermediate position. It will be observed that these latent periods vary as do the incubation periods of the fevers concerned, and it is of interest that in the case of rubella, which has the shortest incubation period and the shortest latent period, encephalomyelitis has developed before the appearance of the rash in an appreciable proportion of cases.

In view of their identical histopathological basis, the close clinical similarity existing between the encephalitic illnesses which complicate these three fevers is not surprising. Indeed, in the absence of the appropriate eruption the individual neurological illnesses are quite indistinguishable, although statistically certain differences are evident. These illnesses may begin abruptly with convulsions followed by coma, or by a slow lapse into stupor following a few hours of headache, vomiting, and restlessness. Impairment of consciousness is the most invariable feature, and in nearly half the cases this amounts to actual coma. Fever is usual, meningism and convulsions common. These are the signs of a general cerebral illness. Signs of focal cerebral damage are infinitely variable. Hemiplegia, tetraplegia, ataxia, retention of urine, optic neuritis, paralysis of cranial nerves, and involuntary movements of various kinds are often encountered. Fatalities are almost limited to patients in coma, and usually occur within the first three days of the illness. Practically all the patients who survive for seven

days recover, and in most of these cases astonishingly few neurological signs remain even when the initial findings indicated massive cerebral damage. Coma, convulsions, and extensor plantar responses are all unfavourable signs, each associated with an increased mortality. The disease is more fatal over the age of sixteen. On the other hand, severe sequelæ (mental defect, behaviour disturbance, or more rarely persisting evidence of focal cerebral damage) are more commonly encountered after illnesses affecting the vulnerable brain of the young child: residual intellectual defect is exclusive to early childhood and has never been recorded in adolescents or adults.

The similarities between these various encephalitic illnesses are evident, but what of the differences? Briefly, chickenpox encephalitis is usually less severe than that associated with measles or rubella. The mortality in chickenpox is 10 per cent. compared with 20 per cent. in the other two diseases. Although occasional instances are more severe than the majority of cases encountered in association with measles, varicella encephalitis is in general a milder illness, with a lower incidence of coma, convulsions, and extensor plantar responses, and a considerably higher incidence of cerebellar signs such as ataxia, nystagmus, and dysarthria. Since the mortality in chickenpox cases which become comatose is comparable to that encountered in similar cases occurring in association with measles, the lower mortality in varicella may be taken as due to the lower incidence of these severe symptoms.

MYELITIS

The myelitis which may complicate any of these fevers is most commonly transverse and mid-dorsal, but occasionally ascending or disseminated. It shows no special features, usually beginning with backache and weakness of the legs, and progressing over the course of a few days through a flaccid to a spastic paraplegia or more rarely tetraplegia. Retention of urine is the rule; an upper level of sensory impairment usual. The condition has a mortality rate of about one in five, death being due to bulbar involvement in the course of an ascending lesion. Most patients, however, begin to improve within a few days or weeks of the onset, and in all except the severest cases (in which actual necrosis of the spinal cord may occur) recovery of function is usually remarkably complete even though the plantar responses may remain extensor for life. Pathologically, demyelination may be focal or disseminated. Especially when the lesion is focal or transverse, thrombosis of a segment of the anterior spinal artery may play a part, possibly on the basis of an allergic arteritis.

POLYRADICULITIS

Polyradiculitis also shows no special features. Painful paræsthesiæ in the limbs herald the gradual onset of a commonly symmetrical flaccid paraplegia with total loss of deep reflexes, muscle pains and tenderness, and sometimes sensory impairment of peripheral or radicular distribution. Cranial nerve palsies are common, and the very rare fatalities which occur are usually due to paralysis of the respiratory muscles. The condition more often progresses

over the course of a few days, and then begins to improve after an apparently static period of a week or two. There are probably two phases of the lesion. Impairment of function is at first due to a rapidly reversible oedematous-inflammatory reaction in the nerve-roots, but this is followed by demyelination of nerve-fibres which is only slowly reparable. At any rate, although recovery is in the end usually complete or almost so, this illness may cause paralytic disability which on occasion remains severe even for a year or more. It is of interest that both myelitis and polyradiculitis tend to be less severe in relation to chickenpox than in measles, whilst all the neurological complications of rubella are at least as severe as those of the latter disease and indeed appear to be somewhat more explosive as well as earlier in their onset.

THERAPEUTIC VALUE OF CORTISONE

The hypothesis that this group of encephalitic, myelitic, and polyradicular syndromes is allergic in nature has already been mentioned, and it is now widely held. It implies that the tissue-reaction involved is not primarily neuronal, as it is for example in poliomyelitis or encephalitis lethargica, but mesodermal and vascular. The initial lesion has been compared to an urticarial weal in the neuraxis, perivascular involvement of neural elements such as axon-sheaths being due to secondary changes such as pressure (as possibly in nerve-roots), or to toxic effusion from damaged blood vessels.

The close similarity of the human lesion to those produced in animals by experimental injection of brain emulsions (experimental allergic encephalomyelitis), and the prevention of these experimental animal lesions by the prior administration of cortisone, were further evidence of a possibly allergic pathogenesis, and encouraged therapeutic trial of corticotrophin and cortisone in the human diseases. The frequent occurrence of dramatic spontaneous recovery renders assessment of results difficult, but arrest of deterioration, rapid restoration of consciousness, disappearance of focal signs, and further therapeutic response of patients who had relapsed when the drug was stopped within a few days of the onset, have all been observed often enough to render coincidence an improbable explanation. Some cases show no response: for example, fulminating hæmorrhagic encephalitis (brain purpura) which may kill within a few hours, and necrotic myelitis. In such instances the lesion is apparently so intense that it may be irreversible from the start. Furthermore, while it could reasonably be anticipated that cortisone might suppress or diminish the exudative-inflammatory reaction which characterizes the early phase of these illnesses, there is no reason to expect any favourable effect on the slow or partial repair of lesions involving established demyelination. I am one of those who consider it probable that the effect of cortisone is in fact what might be anticipated on these theoretical grounds.

Diagnosis must be incontrovertible before undertaking such treatment, but this is more easily achieved in encephalomyelitic illnesses clearly associated with the acute specific fevers than when these occur in the absence

of such an obvious etiological factor, when syphilis, tuberculosis, and poliomyelitis are among the confusing possibilities to be excluded. It must be remembered also that once there is any evidence whatever of spontaneous improvement in these cases this will almost certainly continue. When the diagnosis is clear, and when there is either persisting deterioration or no evidence whatever of beginning improvement, what appears to be a distinct response to the drug will be observed in at least two-thirds of the cases. Sometimes this is dramatic, occurring within a few hours of beginning treatment—a rapid clearing of consciousness in encephalitis or improvement of power and restoration of bladder control in myelitis. By their very nature such observations are uncontrolled, but at the very least arrest and reversal of deterioration are common enough to be highly suggestive. Dosage should be generous, with an average initial amount of 300 mg. daily, gradually reduced over the course of about seven to ten days depending upon carefully recorded progress. No complications have been encountered in over thirty such cases of encephalitis, myelitis, and polyradiculitis personally treated.

MUMPS AND SCARLET FEVER

Encephalitic, myelitic and polyradicular complications in every way clinically similar to those just described occur also in association with mumps and scarlet fever. Pathological evidence is adequate, in the case of mumps at any rate, to establish the apparently identical nature of the lesions. In both diseases, however, these encephalomyelitic syndromes are overshadowed in frequency by other neurological complications of quite different kinds.

The virus of *mumps* is potentially neurotropic, and the short-lived invariably benign lymphocytic meningitis which begins within a few days of the parotitis, and which is the classical neurological complication of the epidemic disease, is usually attributed to virus invasion of the meninges. The fact that such a meningeal reaction is by no means an invariable feature of the less common but more serious encephalomyelitic complications of mumps suggests a qualitative pathological difference between the two orders of complication. Mumps encephalitis appears to have a mortality rate of about one in five.

Neurological complications of *scarlet fever* are frequent, but many of them should really be regarded as sequelæ of complications of the disease. Examples are convulsions, hypertensive encephalopathy, and strokes complicating nephritis; septic meningitis; and cerebral thrombophlebitis. Otitic hydrocephalus—a benign cerebral illness characterized by high papilloedema with disproportionately mild hydrocephalic symptoms—is still a subject of controversy, but there is considerable evidence that its commonest cause is a spreading indolent thrombophlebitis which impairs the absorption of cerebrospinal fluid by mural involvement of the sagittal sinus. Otogenic cerebral abscess is excluded in such cases chiefly by the

finding of a normal spinal fluid, and also by the absence of acute focal electroencephalographic changes: the condition is benign and usually responds to repeated lumbar puncture.

In some ways the most mysterious, as it is the commonest, neurological complication of scarlet fever is a benign lymphocytic meningitis, beginning five to seven days after the onset of the illness, quite unrelated to its severity, and invariably recovering within a matter of days. Whatever may finally prove to be the case in mumps, there is no reason to incriminate a virus in this instance, and such studies have proved repeatedly negative. It should be borne in mind that a lymphocytic effusion is a non-specific reaction of the meninges as of other serous membranes, and does not invariably bespeak virus invasion.

There are only 22 cases of scarlet fever encephalitis on record: they are clinically indistinguishable from the similar syndromes which complicate the other exanthemata, but the fact that 19 patients survived suggests the possibility of a fatality rate more in keeping with that of varicella.

PERTUSSIS

Whatever their etiology or pathogenesis, the neurological complications of pertussis are entirely distinct both clinically and pathologically from all those already described.

These complications are entirely cerebral, neither myelitis nor polyradiculitis having ever been authentically described. They affect predominantly the younger victims of the disease, with a maximal incidence during the first year of life: a feature which at once distinguishes them from perivenous encephalomyelitis, with its predilection for the older victims of the exanthemata previously discussed. Three-quarters of all cases occur between the second and fourth weeks of the illness, but occasional cases are seen in the early catarrhal phase before the onset of paroxysms of coughing. The illness is remarkably stereotyped in form, with generalized convulsions and hours or days of deep coma as almost invariable features. Motor signs are most often bilaterally symmetrical, with extensor plantar responses, but hemiplegia and aphasia occur. The spinal fluid is normal. The mortality is high, especially under the age of two. Some cases manifest decerebrate rigidity, due to virtual decortication. One case in three is fatal, whilst one in three is left with serious sequelæ such as mental retardation, epilepsy, or hemiplegia.

Histopathological changes in fatal cases are often quite inconspicuous. Demyelinating encephalitis is lacking, whilst massive hæmorrhage and air embolism are similarly discounted as pathogenetic hypotheses. The commonest finding is neuronal degeneration maximal in the hippocampus and cerebellum, and possibly anoxic in origin. The striking similarity of the clinical syndrome to that which occasionally complicates pertussis vaccination is immediately evident, but does not assist in defining the possible roles of direct toxicity or sensitization.

THE VALUE OF LOCAL HYDROCORTISONE IN THE TREATMENT OF SKIN DISEASES

BY THE STAFF OF ST. JOHN'S HOSPITAL FOR DISEASES OF THE SKIN,
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HYDROCORTISONE (compound F) has been widely used in the United States of America as a local application, and most reports indicate its usefulness in various kinds of eczema (Sulzberger and Witten, 1952, 1954; Robinson and Robinson, 1954). Reports in this country have been based upon rather small groups of cases and there have been some differences of opinion expressed as to the usefulness of locally applied hydrocortisone (Church, 1955; Morgan, 1955; Russell *et al.*, 1955). The present report concerns a large series of cases observed over a long period, and indicates which skin conditions are most helped. When hydrocortisone has been applied to the skin surface even in large quantities, no evidence of absorption has been forthcoming (Smith, 1953); but in the case of fluorohydrocortisone lotion, recent work (Livingood *et al.*, 1955) suggests that some retention of sodium and fluid may be shown.

SCOPE OF INVESTIGATION

The patients treated in this survey have been under the care of several different physicians at St. John's Hospital for Diseases of the Skin, and data on over 700 cases have been pooled. Only those cases which were thought likely to respond to topical hydrocortisone were included in these trials, so that the cases are strongly biased in favour of a positive response. Most of these patients had eczema of one kind or another. No attempt was made to use locally applied hydrocortisone in patients in whom the disease was extensive, and trials were confined to patients with quite small areas of eczema.

During the early months of these trials comparisons were attempted between similar lesions on opposite sides of the body: the hydrocortisone preparation applied to one side and the unmedicated base to the other. As whatever happens in the skin on one side is usually reflected by similar changes in the other this technique has been abandoned as unhelpful. More information has been gained by following the progress of patients over several months during which the hydrocortisone has been alternated with unmedicated base or with other local applications. Alternatively, if lesions have cleared, frequency of relapse has been followed. In addition some appraisal has been made of hydrocortisone ointments of different strengths.

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The average period of observation for this group of patients was three months, but this average is reduced by a few short-term cases, and many patients were followed for longer (up to one year).

Hydrocortisone acetate in strengths of 2.5, 1, 0.5, and 0.25 per cent. has been used in a base of soft and liquid paraffins and lanolin. Hydrocortisone as the free alcohol has been used in a vanishing cream base in a strength of 2.5 per cent. and of 1 per cent. Hydrocortisone acetate (1 per cent.) has been used suspended in a milky lotion. Outpatients apply these ointments or lotions by gently rubbing in a small amount with the finger for about a minute twice daily.

Diagnosis	Cleared	Im- proved	No help	Worse	Total
Atopic eczema	6	65	27	2	100
Lichen simplex chronicus	4	41	30	2	77
Discoïd eczema	4	57	22	3	86
Ano-genital pruritus (males)	15	33	7	0	55
Ano-genital pruritus (females)	4	26	19	2	51
Specific allergic contact dermatitis	3	19	3	0	25
Eczematous dermatitis of limited extent (unclassified)	3	39	12	2	56
Seborrhœic eczema of limited extent	4	42	8	2	56
Eczema of fingers and hands	0	47	47	6	100
Eczema of pinna including otitis externa	7	32	11	3	53
Angular stomatitis	0	9	6	0	15
Exfoliative cheilitis	1	5	2	0	8
Psoriasis of palms	0	1	7	0	8
Psoriasis of genital region	3	14	1	0	18
	54	430	202	22	708

TABLE I.—Summary of results obtained with hydrocortisone in 708 patients with dermatological lesions.

Results were classified as follows:—

Cleared.—By this is meant that symptoms and signs disappeared completely and did not return when treatment was discontinued for approximately one month.

Improved.—By this is meant relief of itching and reduction of inflammation or complete suppression of physical signs. There was relapse on stopping treatment. In many of these cases hydrocortisone was helpful for a week or two, and often other therapy was needed.

'No help'.—By this is meant that symptoms and signs were unaltered.

'Made worse'.—This indicates that there was irritation and increase of inflammation or of surface infection.

RESULTS

Atopic eczema.—The 100 patients with atopic eczema were of all ages, but most were adolescents and only five were infants. They were treated for prurigo of the face and neck or lichenified prurigo of the flexures at the wrists, elbows or knees, and occasionally for genital lesions. Complete

clearing without relapse on stopping hydrocortisone was uncommon (6 per cent.). A large number (65 per cent.) obtained some symptomatic relief which may have been more than could have been obtained with other therapy. Many patients found the hydrocortisone preparations more effective and more pleasant to use on certain parts of the body (face, neck, genitalia).

Lichen simplex chronicus.—Of 77 adults with lichen simplex chronicus, 53 were women and 35 had the common lichenified patch at the nape of the neck. A little over half of these patients obtained some relief of itching with hydrocortisone, although there might be little or no change in the appearance. Having made some progress with hydrocortisone it was found that more might be gained by turning to tar paste or superficial x-ray therapy. Complete disappearance of the lesion was unusual (four out of 77 cases).

Ano-genital pruritus.—The 106 patients treated for ano-genital pruritus were about equally divided between the two sexes, and it was noticed that the response in males was better than that in females. Of 55 males, 15 were cleared completely and 33 had relief of itching so long as the hydrocortisone was used. Most of these patients had pruritus ani with peri-anal intertrigo, eczema or lichenification only, and the genitalia were involved in relatively few. In the female cases results were less satisfactory in that 21 out of 51 cases were not helped. The pruritus and secondary changes in women tended to be more widespread, involving the vulva and peri-vulval region as well as the peri-anal region.

Specific contact dermatitis.—Twenty-five patients with specific contact dermatitis were found, on patch-testing, to be sensitive to:—

Nickel (14)	Eosin of lipstick (1)	Streptomycin (1)
Nail varnish (3)	Face cream (1)	Chrysanthemum (1)
Paraphenylenediamine (2)	Rubber (1)	Teak (1)

In most of these patients the dermatitis had been present for many months or years, and removal from the material to which they were sensitive did not result in immediate subsidence of the dermatitis. Residual patches of eczematous dermatitis were usually suppressed by the hydrocortisone (22 out of 25 cases). In the more acute, short-exposure episodes, as with hair dye, the influence of hydrocortisone was more difficult to assess, owing to spontaneous recovery.

Discoid eczema.—These patients showed one or a few discoid plaques of exudative eczema, for the most part on the extremities, the condition being chronic and relapsing and presumably constitutional in nature. Because of the difficulty in classifying these cases, some of the patients in this group—for instance, some of those with lesions confined to the backs of the hands—may have owed their eczema in part to non-specific external irritants. Complete disappearance was unusual (four out of 86 patients treated) but improvement was noted in 57 of them. In many of these patients it is remarkable to what extent hydrocortisone may suppress lesions while obviously not curing the condition. Relapse occurred regularly on with-

drawal. Patients with widespread discoid eczema were not included in this series.

Eczematous dermatitis of limited extent.—Patchy eczemas of limited extent, not attributable to contact irritants, form a large but heterogeneous group of 56 cases. Of these, 30 had erythema and scaling of the face and eyelids or of the face and neck. Suppression of the eczema occurred in 39, but complete clearing attributable to the hydrocortisone was apparent in only three cases.

Seborrhæic eczema of limited extent.—Of the 56 patients with seborrhæic eczema, the majority (48 cases) had lesions limited to the neck, face, or ears, the remainder of the group having seborrhæic intertrigo of limited extent. The response was favourable in 46 of these cases. In the two cases which became worse during hydrocortisone applications it was judged that there had been an exacerbation of surface infection.

Eczema of the fingers and hands.—The 100 cases of eczema of the fingers and hands included recurrent vesicular eczema, eczema from non-specific irritants, and scaly dermatitis of the palms. Less than half of these patients were helped by local applications of hydrocortisone and in 6 per cent. of patients the eczema was made worse. Owing to the relapsing nature of these conditions no claim is made for cure, but a few patients received much help from the hydrocortisone at certain stages of the eczema. In general, response in this group of cases has been rather unpredictable.

Eczema of the pinna.—Fifty-three cases of eczema of the pinna, including cases of pruritic scaly eczema of the external auditory meatus, have been treated with hydrocortisone preparations. In seven cases there was complete clearing with no relapse on cessation of treatment and in 32 cases there was subjective relief and the eczema was improved or suppressed.

Angular stomatitis.—In nine out of 15 cases treated the hydrocortisone reduced symptoms and partially suppressed the eczema at the corners of the mouth. Complete resolution did not take place and in six cases the hydrocortisone was not helpful.

Exfoliative cheilitis.—This is an uncommon condition, but an important one on account of its great resistance to treatment. Substantial relief in five cases and complete clearing in one case out of a total of eight, suggest that hydrocortisone ointment is the treatment of choice.

Psoriasis.—Local applications of hydrocortisone have no effect at all on ordinary psoriasis, and palmar psoriasis is no exception. On the genitalia however, where psoriasis is inclined to be moist and pruritic, considerable improvement was seen in 14 out of 18 cases. Complete clearing of psoriasis from the penis was observed in three cases.

DISCUSSION

The data presented in the table are not precise in that the behaviour of eczema is not easily predictable and changes are not measurable. Even the diagnostic grouping of case material is difficult when it comes to separating

one kind of eczema from another. Our experience with hydrocortisone, however, is enough to provide some general appreciation of its usefulness.

In many eczematous conditions locally applied hydrocortisone has proved helpful provided its use has been reserved for cases with a limited extent of the disease. It is not appropriate to widespread eczema and it is of no value in many other dermatoses such as lichen planus and psoriasis vulgaris. Particularly good results are seen in eczema of certain regions of the body such as the eyelids, ears, face and genitalia. As these are regions where most local applications are poorly tolerated, the relief given by hydrocortisone is much appreciated by patients.

Which vehicle should be used depends upon the state of the eczema at the time, although it is remarkable how well the greasy base is tolerated.

In nearly all cases treated, 1 per cent. hydrocortisone has been adequate and it appears to be seldom necessary to use 2.5 per cent. In many instances 0.5 per cent. hydrocortisone ointment has been used successfully. For instance, certain cases of chronic pruritus ani can be maintained symptom free by a small daily application of 0.5 per cent. hydrocortisone ointment.

In about 3 per cent. of cases hydrocortisone appeared to make eczematous lesions worse. Sometimes changing to another ointment base was helpful. Patch testing never showed hypersensitivity to hydrocortisone, but occasionally intolerance to all available hydrocortisone products has been shown. Its complete failure in certain cases which might be expected to respond is unexplained. In a few cases worsening has been due to increased infection, as with *Staphylococcus aureus* infection in seborrhœic eczema. On the other hand, there seems to be little or no evidence that hydrocortisone ointment positively favours superficial infections.

In common with cortisone, hydrocortisone and corticotrophin used systemically for certain inflammatory diseases, hydrocortisone applied locally suppresses inflammation and relieves symptoms without altering the underlying disease process. It cannot, for instance, be expected to protect the skin against irritants and is in no sense a 'barrier cream'. Its value in dermatology is great, but its limitations should be appreciated and it would be a pity if valuable supplies were to be wasted on widespread eczema or on such conditions as psoriasis or generalized pruritus which do not respond.

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THE PROBLEM OF THE STAMMERER

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For practical purposes stammering is best regarded as a symptom of anxiety. If the morbid anxiety can be dealt with, the road is clear for improvement. Even the most distressing stammerer can speak quite smoothly when alone, or when addressing a cat or dog, and usually this immunity extends to speaking to a young child. This shows that it is criticism which he fears, and that his disability is functional and not due to organic defect. His ability to speak depends upon the emotional atmosphere, although in some cases there may be an inheritable vulnerability of the speech complex to stress.

CAUSATION

Stammering begins as a mark of conflict in an insecure personality, and it can become incorporated into the personality as a form of shelter, just in the same way as all neurotic symptoms can come to have value. The primary conflict is the impulse to speak blocked by fear of being wrong.

The eager sensitive child in whom the faculty of speech is a recent development can receive a lasting injury to his self-confidence when he comes running in eager to share some experience and is received by his elders coldly and critically by being switched off the *content* of speech and asked to pay attention to the *manner* of delivery. The sort of thing I mean is:—

'O Mummy, it was so insiting, I——'

'I suppose you mean exciting, and do learn to stand still when you speak'.

Is it surprising that hesitancy in speech occurs henceforth, and more damage is done when mother says to father, 'Have you noticed what a horrid stammer John is getting' and father says 'We must do something about it'?

Once the stammer has occurred and the subject has been made conscious of it as something which arouses disgust and horror the vicious circle of Fear=Tension=Stammer=Fear is well established. The thought, 'I am about to speak', makes the stammerer brace himself as for a high jump. His tensions affect his muscles, preventing coordination and natural breathing and the disproportionate energy he has concentrated overflows into the whole locomotor system. He tries to produce words while inhaling, and struggles the more. The remedy is to relax while in the act of speaking but his tension-producing fears prevent this. Learning relaxation is an important part of speech therapy, but it can only be of limited value unless the ever-present anxiety is efficiently dealt with.

A bullying brother, unsympathetic schoolmaster, an authoritarian father, an over-critical mother, possessive and perfectionist, are apt to figure in the domestic environment and so to confirm a habit of speech which seems to say: 'Don't hurt me'. It is not surprising that the stammer also marks a fear of saying too much. There is a strong aggressive urge which has been

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repressed at the bidding of the super-ego, and through fear of consequences.

A remarkable release of tensions is obtained when the subject is encouraged by the therapist to speak in uninhibited terms of the parent whose over-anxiety has bedevilled his upbringing. As long as it is repressed, the wish to violent self-assertion can continue to create conflict and tensions, and the aggressive urge can be turned against the self so that self-frustration through the stammer becomes an established pattern of living.

The value of the stammer is plainly shown when a hitherto sheltered youngster goes into the wider world of school and being made to feel his insignificance he unconsciously develops or clings to a tendency to stammer as a protection from the demands life imposes. It is in accordance with what we know about the formation of neurotic symptoms generally, that the stammer should have value in terms of the unconscious which represents childish wish-fulfilment. It becomes a crutch which helps him through life and which he cannot relinquish until he has learned to accept reality without compromise.

The stammer is a social handicap and can make him the object of pity or derision, but human nature is such that the individual would rather be remarked for some disability than not be noticed at all, and this attitude can become a substitute satisfaction for real achievement. The stammer forms a protection from responsibilities both at school and in the world of social life, and it enables its possessor to indulge fantasies of the 'if only' type:—'If only it were not for my stammer I could do such wonderful things . . .'. The tragedy is that this is so often true. The stammer often masks an intelligent and capable personality beyond the average, if only the individual can be freed.

TREATMENT

Listeners can help by treating the victim with patience and respect, waiting for him to use his own words and not rushing to 'take the words out of his mouth' even when he seems to be hopelessly choked by them. The stammerer himself must be encouraged to try and express his thoughts in spite of his disability, and not to make it an excuse for remaining in the background. The speech therapist has an important role in giving him opportunity and courage, but the psychotherapist is needed to deal with the tangled unconscious factors.

As with all neuroses the best 'treatment' is prevention and parents must beware of turning a passing phase into a lifelong habit by subjecting the child to the withering blast of their own anxiety. In this prophylaxis the family doctor has an important part to play in teaching parents how to deal with a sensitive over-anxious child and explaining that a tendency to stammer is not something for the expert to eradicate like a diseased tonsil, but is a reaction to an environment which lacks an atmosphere of security. The parents should cultivate a distinct and unhurried form of speech while always taking it for granted that the child will outgrow his difficulties provided the searchlight of criticism is not used to show them up more plainly.

GENERAL PRACTITIONERS' FORUM

SULPHONAMIDES AND ANTIBIOTICS IN GENERAL PRACTICE: A STUDY OF THEIR USE AND ABUSE

By EDWARD D. FOX, M.B., B.S.

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THIS article is an attempt to assess the degree of use of sulphonamides and antibiotics in general practice. These drugs are used freely and often indiscriminately for a wide variety of conditions, many of which underwent spontaneous resolution in the days before this powerful chemotherapeutic and antibiotic armamentarium was available. Necessarily, such a study must be preceded by a study of morbidity which involves recording attendances by, and visits to, patients as well as the actual illnesses themselves.

The study has been made in a practice in a semi-industrial town of 12,000 inhabitants, in which about 5 to 10 per cent. of the doctor's work is in rural areas. It cannot be stressed too strongly that this is an individual study involving statistically insignificant numbers and that the results of the use of the various drugs are obviously a personal reflection of the author's prescribing habits. It is hoped, however, that it may serve to stimulate more valuable work in this important field. A similar study has recently been made by Fry (1956).

The survey covers 770 patients in the year February 1, 1954, to January 31, 1955, of whom 321 (41.7 per cent.) received sulphonamides or antibiotics.

METHOD OF RECORDING MORBIDITY

If all consultations (attendances at surgery) and visits for a given condition are recorded this gives an index of the relative frequency with which doctors are consulted for given conditions. This, however, as Horder and Horder (1954) have pointed out, gives a *false index of morbidity*. The *true index of morbidity* is measured by recording only the first consultation and/or visit for a given condition. An example will clarify this:—

A patient with tonsillitis may attend surgery twice and be visited four times at home; this can be recorded thus:—

False index of morbidity	A (attendances)	= 2
	V (visits)	= 4
True index of morbidity	A	= 1
	V	= 1

In this study both indices of morbidity were recorded as a matter of interest but, in my opinion, only the true index is of real value. Logan (1953, 1954), in a comprehensive study of morbidity in eight different general practices, primarily records the false index of morbidity but supplies the corrective by also recording the total number of patients attending.

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MORBIDITY INDICES IN THE GROUPS STUDIED

In the 449 patients who did not receive sulphonamides or antibiotics (group A) the figures were as follows:—

False Index A = 1574 (male 771; female 803)
V = 282 („ 116; „ 166)
True Index A = 561 („ 298; „ 263)
V = 151 („ 52; „ 99)

From the true figures the following can be calculated:—

- (i) Average number of attendances per patient = 1.24 (561/449)
- (ii) Average number of visits per patient = 0.33 (151/449)

Age-group	Male	Female	Total
0-5 years	52	45	97
6-9 „	39	24	63
10-19 „	15	20	35
20-29 „	14	11	25
30-39 „	17	14	31
40-49 „	11	9	20
50-59 „	11	11	22
60-69 „	11	5	16
70+ „	6	6	12
Total			321

TABLE I.—Use of sulphonamides and antibiotics by age-groups. The figures relate to the numbers of patients.

In the 321 patients in whom the drugs were used (group B) the results were as follows:—

False Index A = 998 (male 540; female 458)
V = 409 („ 211; „ 198)
True Index A = 398 („ 283; „ 115)
V = 208 („ 115; „ 93)

From this it can be calculated that the average number of attendances per patient was 1.23 (398/321), whilst the average number of visits per patient was 0.64 (208/321). These figures emphasize the fact that, generally

Drug	S	P	C	St	Au	E	Totals
Female	113	58	34	2	3	1	211 times used
Male	120	99	40	2	3	4	268 „ „
Totals	233	157	74	4	6	5	479

TABLE II.—Individual analysis of the use of sulphonamides and antibiotics in 321 patients.

S = sulphonamides
P = penicillin
C = chloramphenicol
St = streptomycin
Au = chlortetracycline
E = erythromycin

The 321 patients consisted of 145 females and 176 males. The rate of use of the drugs in the male is thus 1.52 (268/176) and in the female 1.45 (211/145) times per patient.

speaking, patients of group B were iller than those of group A, and it is seen that the visiting rate of 0.64 visit per patient is double that in the other group. The attendance rate is seen to be the same in both groups A and B and this is accounted for by the fact that convalescent patients

can attend surgery after the acute phase of the illness.

As the survey covers the period from February 1954 to February 1955, and the newer antibiotics, such as chlortetracycline, oxytetracycline, tetracycline and erythromycin, were only released for use by general practitioners in November 1954, this fact naturally influences the histogram pattern as seen in fig. 1.

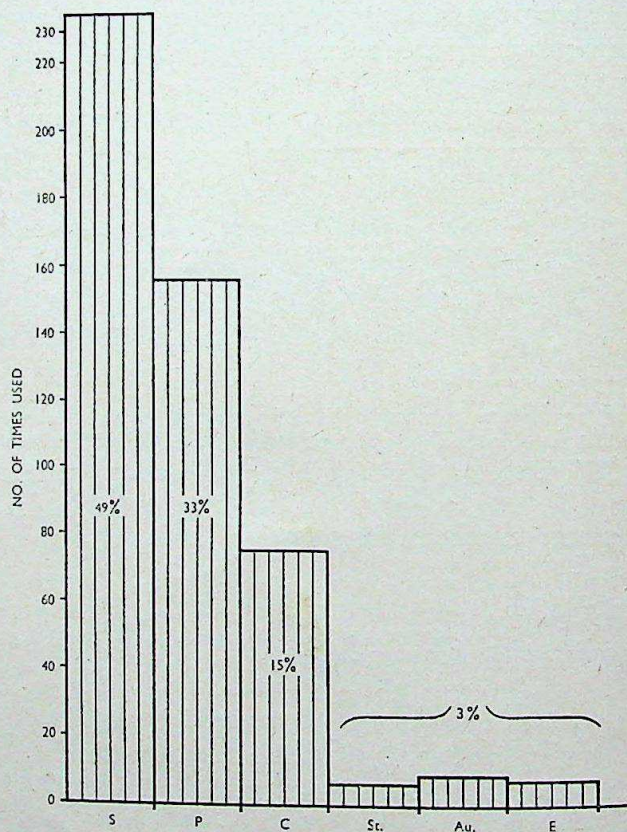


FIG. 1.—Histogram showing the proportionate use of the sulphonamide and antibiotic drugs. Figures in the columns express the percentage use related to the 479 times the drugs were used all together.

S = Sulphonamide. P = Penicillin.
C = Chloramphenicol. St = Streptomycin.
Au = Chlortetracycline. E = Erythromycin.

AGE-GROUPS

Reference to fig. 2 will show that the drugs were used largely in the age groups 0 to 5 years and 6 to 9 years. Out of a total of 321 cases, 160 lie in these two groups, giving a value of 50 per cent. of total use for children under ten years of age. Table I shows that the drugs were used in only 12 patients over 70 years of age. There is no doubt that in a larger survey this age-group, as every general practitioner knows, would contain far more patients and the use of the drugs would thus be proportionately greater.

DRUGS USED

The drugs were prescribed a total of 479 times (table II) and the histogram (fig. 1) shows diagrammatically the proportionate use of each individual drug with the actual percentage use in brackets in the columns.

DISEASE INCIDENCE

Table III shows the striking incidence of respiratory diseases as classified here (45.8 per cent.). Although the classification in this group is slightly

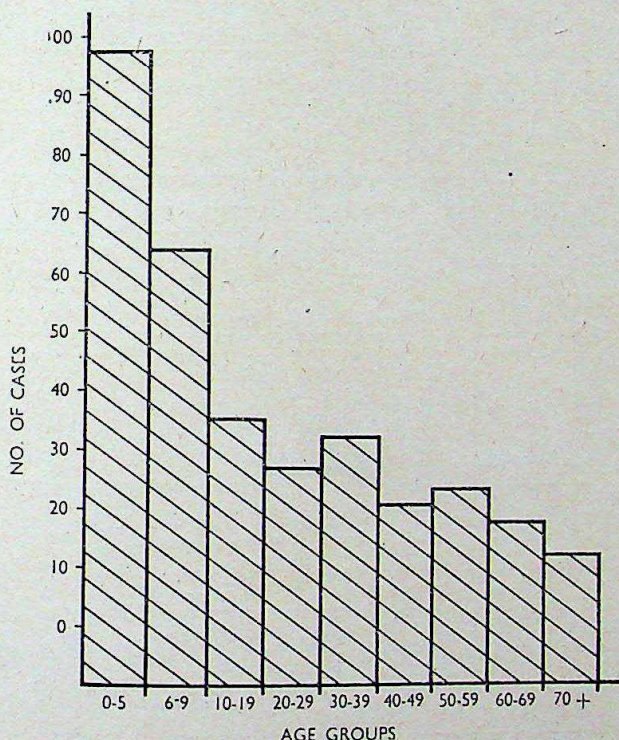


FIG. 2.—Histogram showing the use by age-groups of the sulphonamide and antibiotic drugs. Total number of patients surveyed=321.

different from that adopted by Horder and Horder (1954), Logan (1953, 1954), McGregor (1950) and Fry (1952), my findings confirm theirs: that the most frequent causes of ill health in all age-groups were respiratory and upper respiratory tract infections.

The individual analysis of the use of the drugs and fig. 1 show that in this survey sulphonamides were used more than penicillin which in turn was used more than chloramphenicol. Streptomycin, chlortetracycline and erythromycin were scarcely used and I do not feel that the percentage use would have been much higher had the latter two drugs been available for the whole year of the survey. The use of streptomycin in general practice appears to be confined almost exclusively to tuberculosis, renal infections, occasional bowel infections such as appendix abscess, and cholecystitis.

Diseases	Male	Female	No. of cases	Total
<i>Respiratory diseases</i>				
Coryza	1	3	4	207 (45.8%)
Sore throat	1	4	5	
Tonsillitis (inc. quinsy)	40	25	65	
Laryngitis	—	5	5	
Bronchitis	50	39	89	
Pleurisy	5	3	8	
Pneumonia (all forms)	6	6	12	
Bronchiectasis	—	1	1	
Influenza	7	9	16	
Sinusitis	2	—	2	
<i>Inflammations</i>				
Boils, abscesses, carbuncles	17	12	29	44 (9.7%)
Septic spots	3	3	6	
Cellulitis	4	4	8	
Mastitis	—	1	1	
<i>Vascular diseases</i>				
Venous thrombosis	—	1	1	1
<i>Ear diseases</i>				
Otitis externa	2	2	4	26 (5.7%)
Otitis media	8	7	15	
Otorrhœa	5	2	7	
<i>Skin diseases</i>				
Herpes zoster	1	—	1	14 (3.1%)
Eczema (infected)	5	1	6	
Impetigo	2	3	5	
Moniliasis	—	1	1	
Undiagnosed rash	—	1	1	
<i>Eye diseases</i>				
Conjunctivitis (+ styas)	15	11	26	33 (7.3%)
Blepharitis	3	1	4	
Uveitis	1	—	1	
Foreign body	2	—	2	
<i>Infectious diseases</i>				
Measles	—	1	1	59 (13%)
Pertussis	18	19	37	
Varicella	—	2	2	
Mumps	8	11	19	
<i>Gastro-intestinal diseases</i>				
Gastroenteritis	9	5	14	28 (6.2%)
D. & V.				
Gastric chill				
Stomatitis	3	3	6	
Appendicitis	1	—	1	
Teething	3	4	7	
<i>Renal diseases</i>				
Cystitis	—	6	6	9 (2%)
Pyelitis	1	2	3	
<i>Lymphatic diseases</i>				
Enlarged cervical glands	1	3	4	4 (0.8%)
P.U.O.	14	5	19	19 (4.2%)
<i>Injuries</i>				
Cuts	3	—	3	7 (1.5%)
Burns	2	—	2	
Bites	1	1	2	

TABLE III.—Disease incidence in 321 patients receiving sulphonamides or penicillin

The results confirm the view that in the prescribing of the drugs under survey the order of use should as a rule be sulphonamide first, followed by penicillin and chloramphenicol and only then by the more powerful drugs. Naturally, the proviso must be made that when an organism causing a disease is known to be insensitive to a particular drug then that drug is

Disease	S	P	C	St	Au	E	Total times used	No. of cases of disease
Tonsillitis + sore throat	40	25 (18)	3	—	—	3	71	70
Bronchitis	74	14 (8)	10	—	1	1	100	89
Pleurisy	8	—	—	—	—	—	8	8
Pneumonia	3	11 (2)	1	—	1	—	16	12
Influenza	14	2 (1)	1	—	—	—	17	16
Boils and abscesses	6	29 (7)	1	1	1	—	38	35
Cellulitis	2	9	—	—	—	1	12	8
Otitis media	3	12	4	—	—	—	19	15
Otitis externa	1	2	2	—	—	—	5	4
Otorrhoea	2	1	6	—	—	—	9	7
Conjunctivitis	6	23	2	—	1	—	32	30
Impetigo	—	5	—	—	—	—	5	5
Pertussis	2	1	34	—	—	—	37	37
Mumps	18	1	—	—	—	—	19	19
Gastrointestinal upsets	14	—	—	—	—	—	14	14
Stomatitis	2	4 (1)	—	—	1	—	7	6
Teething	7	—	—	—	—	—	7	7
Cystitis and pyelitis	8	—	1	1	—	—	10	9
P.U.O.	16	6 (5)	1	—	—	—	23	19

TABLE IV.—Analysis of the use of sulphonamides and antibiotics for the principal diseases encountered. The less important diseases have been omitted from this table.

S = sulphonamide

Au = chlortetracycline

P = penicillin

E = erythromycin

C = chloramphenicol

The figures in brackets in the penicillin column refer to the number of times oral penicillin was used.

not exhibited and the first and least complicated antibiotic to which the organism is sensitive is used. For example, outside hospital, *Staph. aureus* is known in most cases to be sensitive to penicillin. Hence a carbuncle would be treated first and foremost with penicillin.

There is a tendency in general practice to prescribe the group of drugs released in November 1954 (e.g. chlortetracycline, tetracycline, oxytetracycline) indiscriminately and in the 'knock them out with something powerful at the start of the illness' attitude. This is bad medicine, easy to do and will lead inevitably to the birth of even more resistant strains of microbes.

DETERMINATION OF DRUG SENSITIVITY

There is thus seen to be a strong case for determining bacterial sensitivity to these drugs before therapy of any kind is instituted. It is conceded that this is very much easier and more practical in hospital than in general practice where in fact it is often impossible, but general practitioners must be aware of the potential dangers of large-scale prescribing of these expensive and powerful drugs even if the 'blunderbuss treatment' tempts and works.

DISEASES IN WHICH EMPLOYED

The drugs were used 100 times in 89 cases of bronchitis (table IV). Penicillin (14 times), chloramphenicol (10 times), chlortetracycline (once) and

Group	Male	Female	Total times used	% use
0-5 years	14	6	20	87
6-9 "	9	6	15	
10-19 "	4	4	8	
20-29 "	—	—	—	
30-39 "	1	2	3	13
40-49 "	—	—	—	
50-59 "	1	1	2	
60-69 "	1	—	1	
70+ "	—	—	—	
Totals	30	19	49	100

TABLE V.—Use of oral penicillin by age-groups.

erythromycin (once) were only employed when inadequate response to the sulphonamide existed. As streptococcal sore throats and tonsillitis usually respond better to penicillin than to the sulphonamides, the high utilization of the latter (40 times out of 71) is to be deprecated.

The empirical use of sulphonamides, as in this survey, in cases of coryza, influenza, mumps, odd rashes, pyrexia of unknown origin and teething is to be deprecated. During the summer of 1955 I treated over 100 cases of

Disease	No. of times used	Disease	No. of times used
Coryza	2	Boils	7
Tonsillitis	18	Undiagnosed rash	1
Bronchitis	8	Measles	1
Laryngitis	1	Stomatitis	1
Pneumonia	2	P.U.O.	5
Influenza	1	Injuries (burns)	2

TABLE VI.—Diseases for which oral penicillin was employed. An analysis of the 49 cases in which oral penicillin was used.

measles. In half of these sulphonamides were used prophylactically and in the other half a simple aspirin mixture. The only complication (bilateral otitis media) arose in a case receiving sulphonamides. It is still an open question whether these drugs should be used prophylactically or blindly in some diseases. A report by a study group of the College of General

Practitioners (1956) states that there is nothing to recommend the routine use of sulphonamides in measles, since this increases rather than reduces the total complications rate.

From table IV it will be seen that 14 cases of gastro-intestinal upset (D and V, gastroenteritis, 'gastric chills') were successfully treated by sulphonamides alone and that there was no indication for their increasingly common use in combination with antibiotics.

The highest use of *chloramphenicol* was for pertussis, which was justified by the clinical response obtained. This drug is used empirically, freely and wrongly for cases of otorrhœa—many of which would settle if the basic pathology were investigated and treated simply.

ORAL PENICILLIN

Penicillin in all forms was used a total of 157 times. Oral penicillin was employed in 49 cases (30 males, 19 females). Thus 31 per cent. of all penicillin used was in the oral form. Of the oral penicillin, 87 per cent. was used in the 0-9 years age-group (table V) and this mostly for cases of tonsillitis and bronchitis (table VI).

In 10 out of the 49 cases in which it was used the penicillin was in the form of a tablet in combination with another (non-antibiotic) drug ('pen-benemid'). 'Neolin', 'penidural' and 'eskacillin' were used in the remaining cases. It is my experience that most cases of tonsillitis in young children can be effectively treated with oral penicillin. This has been well confirmed since penicillin V has been available in general practice. This preparation gives blood levels higher than any other oral penicillin.

DISCUSSION

It must be emphasized that before 1935 sulphonamides did not exist and before 1945 neither did penicillin (except for hospitals and the Services). The remaining antibiotics are all post-1945 developments. General practitioners must hold themselves in check and remember these facts when tempted to use 'blunderbuss treatment' for simple or indeterminate illnesses in order to 'save time'. Their time would be better saved by taking swabs in order to determine the sensitivity of a particular organism, and public money would be saved by using the cheapest drug which works when the sensitivity has been discovered.

We must never forget that people recovered from even serious illnesses before our wonderful armamentarium of modern drugs and the more modern antibiotics even existed.

Finally, I should like to stress the fact that this is a statistically insignificant study which directly reflects the usual prescribing habits of one general practitioner. Such a study is always bound to be personal in this way, but it is hoped that it may stimulate others to make larger studies in this important field. General practice is a more fertile research ground than any other which exists in clinical medicine and the best researches often spring from the simplest ideas.

SUMMARY

A study is presented in which morbidity in general practice is briefly analysed.

The exhibition of sulphonamides and antibiotics is analysed in detail and variations of use with age, type of illness and method of administration have been recorded.

In general it can be said that patients in whom these drugs are used are more ill than those in whom they are not employed.

The study shows that sulphonamides and penicillin are the most frequently prescribed drugs for the commoner conditions.

Respiratory and upper respiratory diseases accounted for 45.8 per cent. of all the illnesses seen.

My sincere thanks are due to Drs. Douglas Wilson, J. Fry, Ian Munro, and R. J. F. H. Pinsent who gave me most helpful advice and constructive criticism when I first thought of this study. Without their stimulus this small study might have remained in its embryonic state.

I have also to thank my wife for the tolerance, good judgment and incentive which she has provided all the time, but especially during the more arduous parts of this study.

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PERIPATETIC RHEUMATIC HYDROARTHROSIS

By G. B. KIRKLAND, M.R.C.S., L.R.C.P.

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We all have our 'interesting' cases. To decide which is our 'most interesting' case is often difficult, but I have little doubt that the following case falls into this category so far as I am concerned.

CASE RECORD

The patient—call him George—first came to me four years ago with the equivocal remark: 'I'm about due for another of my attacks'. When asked of what, he replied: 'That is just the trouble: nobody knows'. He proceeded to produce a diary and to read therefrom an impressive list of those who had treated him without success over a period of more than twenty years.

A careful clinical examination at the time produced no evidence of abnormality in any system. Extensive x-rays of the joints showed no bone changes, and reports on the blood count, the erythrocyte sedimentation rate and the liver function were all normal. But the threatened 'attack' duly eventuated.

George went to lunch at midday. After the meal he experienced nausea and malaise and vomited. He drove home, a matter of twelve miles. I saw him at seven that night. He was clearly in considerable pain. The left knee joint was grossly swollen, markedly erythematous and obviously full of fluid. The pulse was 100 per minute and regular. The blood pressure was 160/70 mm. Hg, and the temperature was 98.4° F. (37° C.). He was pale, anxious and sweating profusely. Fluid was aspirated under considerable pressure from the knee. This was pale brown in colour with a specific gravity of 1.000. The laboratory report was: 'Sterile. No traceable elements. Very scanty leucocytes'.

He was put to bed and given large doses of codeine and salicylates. The following morning the knee was still very swollen but the erythema and pain had gone. George said he had had a bad night on account of the pain and felt exhausted. Twelve hours later the joint was normal. There were no œdema and no signs that anything unusual had occurred. The following morning he returned to work.

He said that he got similar attacks irregularly at about five or six weeks' intervals in either a knee or an elbow. He remembered rare attacks in the ankles, but never in any other joint. This recurrent syndrome had persisted over twenty years despite every kind of treatment.

DISCUSSION

Here is a case of a wandering joint syndrome: swelling, massive effusion of sterile fluid, erythema, pain, nausea, vomiting and rapid subsidence without residual symptoms, unaccompanied by any systemic abnormality which we could trace. I have seen a few similar cases in the Tropics, and American medical journals have scanty references to allied conditions.

I suggest that an appropriate diagnosis is 'peripatetic rheumatic hydroarthrosis', and that it is an extremely rare disease.

Since the first 'attack', which I saw, he has carried with him cortisone tablets and takes two immediately he feels the first sign of onset. So far, i.e. for four years, this treatment has been immediately successful and no 'attack' has developed. George says that the premonitory signs are becoming progressively less frequent. To date he has not had any for four months. He has, however, just come out of hospital having had glandular fever, but I fail to see any connexion between this and his freedom from his 'attacks'. How long his cortisone treatment will continue to be successful is a moot point. Is it wishful thinking to imagine that the condition may eventually clear up?

EVALUATION OF A NEW ANTI-TUSSIVE

By CLIFFORD T. ROBERTS, M.D.

Leeds

DURING last summer I investigated in infants and children the cough-suppressant qualities of a preparation of the citrate of the diethylamino-ethoxyethyl ester of α : α -diethylphenylacetic acid, known as 'oxeladin'. This group of patients was selected since the 'coughing child' is a perennial problem and it would therefore be possible to conduct a survey during the summer months when more time would be available to follow-up the cases.

The preparation was presented in the form of a palatable linctus containing 10 mg. of 'oxeladin' in each teaspoonful (4 ml.).

SCOPE OF INVESTIGATION

The main criterion in the selection of cases was, of course, the desirability of suppressing the cough and therefore the clinical examination was first directed to excluding those patients who, because of an active infection in the chest, were in primary need of sulphonamide or antibiotic therapy. Cases with few physical signs in which nevertheless there was suspicion of a significant pulmonary lesion were referred to a chest clinic for further investigation. Attention was paid to the presence of any focus of infection outside the chest, especially the nasopharynx, and priority was given to mopping-up any such septic foci. The residuum consisted of a group to which an exact diagnostic label was difficult to attach but who had a cough as the common denominator with few physical signs on auscultation.

The patients ranged in age from 1 year 5 months to 11½ years, with a corresponding scale of dosage from 2 ml. thrice daily to 4 ml. twice daily. The individual dosage in two cases was varied by the child's known tolerance of anti-tussive mixtures and it so happened that in both these cases it was considered advisable to give a larger dose than the normal weight and age ratio would indicate.

RESULTS

In all, 35 children were considered suitable and the results achieved could be roughly classified into four groups: (a) Successful—26 cases. (b) Slight improvement—4 cases. (c) Failures—4 cases. (d) Allergic reaction—1 case.

(a) The most remarkable feature about the children in this group was the number who showed a dramatic improvement in only three to four days. Ten of the children became sign- and symptom-free within this period and only four patients in this category required a continuance of treatment beyond seven days. In at least two cases in this group the child acquired some intercurrent infection during treatment without any apparent diminution in the effectiveness of the anti-tussive preparation.

(b) The classification of slight improvement was reserved for those patients whose cough was diminished but still very troublesome and a definite domestic problem. Into this group went two children who slowly improved but whose eventual recovery was achieved by a *National Formulary* antispasmodic mixture.

(c) Two of the four failures were established cases of pertussis who had earlier been treated with antibiotics followed by antispasmodics, e.g. atropine methonitrate drops, and who eventually had to be admitted to hospital because of bad home conditions and lack of facilities.

(d) One case has been classified as having an allergic reaction. After two days' treatment urticaria and vomiting occurred and the preparation was immediately withdrawn. The home conditions and general domestic hygiene

were, however, so bad in this case that it is impossible to be certain that it was not produced by other causes.

Administration of the preparation was facilitated by its marked palatability, and the cooperation of the parents was encouraged by the absence of any such side-effects as drowsiness, anorexia or constipation.

CONCLUSION

This short series of cases was sufficient to give grounds for believing that 'oxeladin' will be a formidable recruit to the ranks of anti-tussive drugs.

I am indebted to British Drug Houses Ltd. for making available a generous supply of 'oxeladin' in the form of 'pectamol' linctus.

A MORNING IN A DOCTOR'S SURGERY

BY A PATIENT

I AM always filled with a feeling of timidity when I enter a doctor's waiting room. I know that when I enter the eyes of all those who have got to the waiting room before me are focused upon me. All those mouths seem to be saying 'I wonder what's wrong with him—he looks all right', and I feel like answering back, 'You can never judge a book by its cover'.

FULL HOUSE

It is a very busy morning for the doctor and every seat is occupied as I enter the waiting room. So I find a corner to stand in. Immediately I settle in, the other occupants of the room seem to lose interest in me, and they carry on with their various interests. Some are looking at old magazines they have taken from the table, others are gazing at the floor, and look as though they are deep in thought, whilst some are in earnest conversation with their immediate neighbours and from snatches of the talk I hear most are suffering from every complaint known to medical science.

A small boy becomes tired of waiting and wants to use the waiting-room floor as a playground and is promptly grabbed by his mother and told to be quiet, for otherwise how did he think the doctor could listen in to people's chests with his tubes. Suddenly the doctor calls out 'Next please'. Instantly a murmur goes round like the noise made by a swarm of bees. 'Won't be long now, he's made a start', they whisper to one another. I notice that at this point the patients look suspiciously at all around the room, and I know they are summing up as to whose turn it is next.

THE KNOW-ALLS

In the meantime I have occupied the seat left vacant by the first patient. I find myself wedged between two very stout ladies. Immediately they start talking across me. 'Ain't you so well ducks this morning?', queries one lady.

'Didn't see you here last week'. Back comes the reply: 'No dear, I didn't feel well last week, so didn't make the journey'. I pondered over this reply for it seemed strange to me that she should come to the surgery when she felt well. Then there was silence, and I could sense that they were lip-talking to one another, and guessed the conversation was only for female ears. I felt a little red under the collar and hid my face behind my newspaper. Then the conversation became normal again. 'Did yer look in at the Telly last night—that programme about cancer of the lung and smoking. After the doctors had had their say I told my old man straight, if he didn't give up smoking—he had had it. And do you know what he said? He would sooner have had it than give up his fags. These men want some understanding don't they?'

'Next please', called the doctor. A youngish woman got up. As soon as she had entered the consulting room my two companions started again. Nodding her head towards the doctor's room one of them said: 'She's going to have her first baby'—goodness knows how she got this news—'always talking about it', she continued, 'Wait until she is like me, had ten nippers and reared the lot, she won't be so fussy'.

IF LOOKS COULD KILL

The next call from the doctor started a rumpus, for two patients got up at the same time: an old man in his late sixties and a demure young lady. 'It's my turn lady', said the old boy—cunningly edging towards the doctor's room. 'It certainly isn't', said the young lady, 'I was here long before you' and she appealed to the other patients, but by this time the old chap was in the consulting room and the door had closed. He had won the day. But if looks could kill when he came out he would have dropped dead by the look the young lady gave him as she passed on her way to see the doctor.

Two men opposite me were discussing which horse was going to win the 2.30 that afternoon. I saw a coin pass with a request for a bob each way.

In the corner of the room was a young girl with a woman whom I presumed to be her mother. The girl was quietly crying and the mother was giving her some loud advice which I could distinctly hear. 'You tell the doctor everything—hold nothing back'. This seemed to increase the girl's tears. Anyway when the girl and her mother came out of the consulting room the girl was smiling and I presumed all was well. The doctor had brought laughter to a sorrowful heart. A voice across the room addressed all and sundry: 'Blimey, I hope he's going to get a move on', meaning of course the doctor, 'Got to get my old man's dinner on, he's home at one'. Her remarks were met with silence.

My turn to see the doctor eventually came and after my consultation I passed from the waiting room just like a ship that passes in the night—thinking to myself that I had seen enough characters to make a full-length film at any cinema show,

HYDROTHERAPY AT A NORTHERN SPA IN THE EIGHTEENTH AND NINETEENTH CENTURIES

By O. B. APPLEYARD, M.D.

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'Drink, my children; health consists in the pliability and moisture of the parts. Drink water by the pails-ful, it is a universal dissolvent; water liquefies all the salts. Is the course of the blood a little sluggish? this grand principle sets it forward; too rapid? its career is checked'. (*History of Gil Blas*)

ABOUT 1620, the russet-coloured water of a Scarborough spring aroused the curiosity of a Mrs. Farrow, a resident and a 'discreet Gentlewoman'. She so far let her discretion be overcome by valour that she tasted some, and noted an acid taste. The gossips soon decided that a flavour so unpalatable must be associated with medicinal properties and, as hydrotherapy was then increasing in general popularity in England, Scarborough was qualified to become a fashionable spa.

PRINCIPLES AND PREJUDICES

This process took about 150 years and was greatly assisted by the literary expositions and wranglings of such medical gentlemen as had an axe to wield or to grind. One of the most obstreperous was Dr. Robert Wittie of York, a firm believer in the old humoral pathology and the efficacy of Scarborough Spa water. Dr. William Simpson, a younger towns fellow, not only preferred chemistry to alchemy, but on occasion the Harrogate Spa waters to those of Scarborough.

This lack of discrimination provoked Wittie, in 1669, into an attempt to restore what he called 'the Peace of the Faculty' by addressing Simpson as 'a Fierce Chymical Pretender . . . an Upstart . . . stuff'd with Bombast . . . who, if [he] catch a Fever in earnest and manage it according to his present Opinion . . . he will become felo de se and forfeit his Goods and Chattels to the King'.

Simpson in turn rebuked Wittie for his 'Calumnies, Taunts, Scoffs and groundless Accusations', and, 'We will', he said awfully, 'examine his deposited Principles of this Mineral Spring'. The examination took up a good deal of Simpson's 'Hydrologie Chymica' (1669) and resulted in the examinee being heavily ploughed, Simpson concluding infuriatingly that 'it is now time, after the unhinging of Dr. Wittie's Principles, to make a serious scrutiny into the real Principles of this Spaw'.

Dr. George Tunstall ('Scarborough Spa Spagyrically Anatomised', 1670) presumed to write as 'a friend to both' antagonists, with the result that they both attacked him, although he had troubles enough already. In 1661 he had been cut for the stone by 'the famous fortunate Chyrurgeon Mr. Thomas Holiard of London', and wished to analyse Scarborough Spa waters to

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determine whether or not they encouraged the formation of urinary calculi. The specimens of water bottled for him contained so much sand that he suspected carelessness in the servant who collected them. Tunstall's

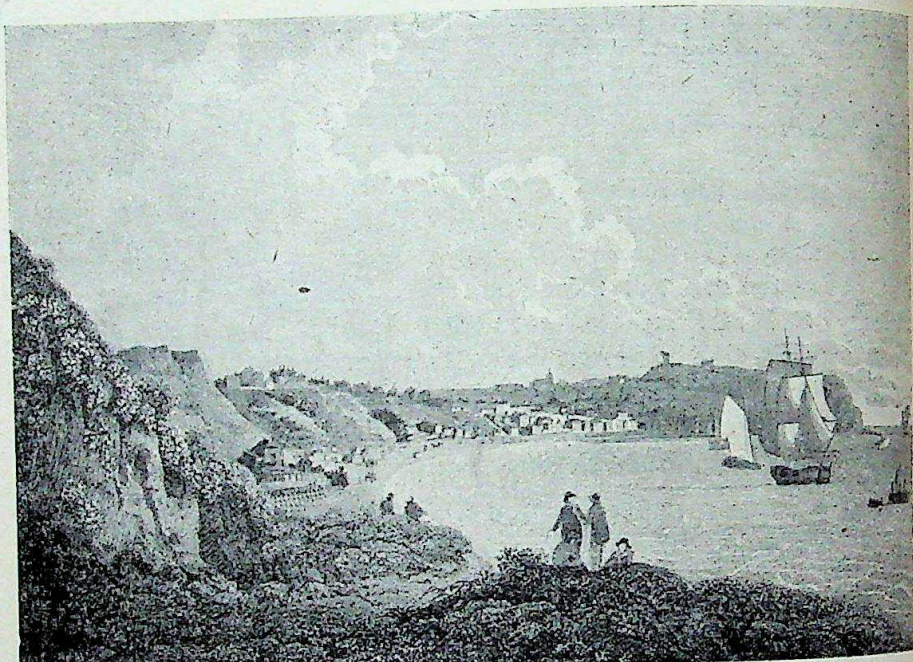


FIG. 1.—Scarborough in 1799.

conclusion that 'the Nature of Scarborough Spaw waters is petrifying'—which might also be said of the temperature of Scarborough sea-water—was scorned by Simpson but drove Wittie to frenzy. Tunstall was no help when he told how, despite Wittie's claims that Scarborough waters cured practically everything, when he called on Wittie in York 'after Spaw time', and asked him 'how the waters did with him, he gave me no answer but that he was very ill'. Tunstall decided: 'I became his enemy for telling him the truth', and, rounding on Simpson, prescribed for him 'some further experience in his laboratory and a little more time in his library'.

Dr. Thomas Short went one better in his 'History of Mineral Waters' (1734), being illiberal enough to insert in the Index such entries as:

- 'Errors in Examining Mineral Waters, Dr. A's,
- 'Errors and Prejudices in Examining Mineral Waters, Dr. B's.,
- 'Mistakes in Examining Mineral Waters, Dr. C's.,
- 'Scanty and Inconclusive Examination of Mineral Waters, Dr. D's., etc.,

a catalogue whose intolerance suggests that Dr. Short's liver might have benefited by a course of Spa waters.

In contrast it seems quite an achievement for non-belligerents such as Shaw (1734), Linden (1748), Russell (1753), Alexander (1839) and Breary (1849) to have written and lectured on mineral waters and hydrotherapy without greatly offending anybody.

SEA-BATHING AND GAMING

In addition to the novelty of using water for drinking, Scarborough offered the exciting new venture of sea-bathing, as practised by Royalty in the South of England. The number of visitors increased yearly, until by the end of the 18th century Scarborough was described as 'romantic . . . and exhibits all the refined amusements of polished life'. The population was then 8000 to 9000, and the amusements, refined and otherwise, were exhibited as hydrotherapy, with 'raffling and gaming', and 'Balls every evening . . . a Pharo bank, a hazard table and fair chance' in the Long Room. One susceptible visitor was almost overwhelmed by the Scarborough Long Room, which he found 'very superb . . . noble', with its twelve chandeliers quite outshining the 'Spaw Rooms' which had 'a very naked and scurvy appearance'. Presumably Pharo, hazard and fair chance were fairer to the banker than to the speculator.

Following upon the visitors came a migrant from London, Dr. Robert Knox, Physician to the Middlesex Hospital (1769), who attended Scarborough 'during the Bathing Season'. It is not known what the indigenous medical practitioners 'all of high character and reputation' thought about this cattle-reiving, but the 'New Scarborough Guide' of 1797 said severely;

'It is unnecessary for them (i.e. Physicians) to write out every article of a prescription at full length as the Scarborough apothecaries are men of education and literature'.

PEERS AND COMMONERS

The industrial revolution was at this period producing a wealthy and vigorous middle-class; better roads, curiosity, the rulings of Fashion and, to a lesser extent, metabolic disorders brought these people, and the northern aristocracy, to Scarborough for the spa season.

To encourage the faint-hearted, Dr. Peter Shaw (later Physician in Ordinary to George III, and not disinterested, as he practised and 'read Chymical lectures' in Scarborough) thoughtfully pointed out (1734):—

' . . . these waters [at Scarborough] formerly known to few, and healing chiefly the sick of inferior rank, are . . . introduced into Better Company and now cheer the Spirits and Brace the Nerves of Peers as well as commoners'.

The spirits and nerves of the entire hierarchy of invalids should have been further fortified by Shaw's quotation from Sir John Floyer:—

'Cold Bathing has this Good Alone,
It makes old John to hug old Joan'.

It is not clear whether the hugging was after the manner of King David and Abishag the Shunammite, or for a purpose more ambitious, but the couplet was excellent 'box-office'. Likewise (the hangover being no respecter of rank) Shaw's prescription of hydrotherapy as a prophylactic against 'Diseases of the Head . . . Hiccoughs, Burning Heats and Thirsts . . . common to High Living'.

In 1737, Frances Sitwell sent a servant from Renishaw to Scarborough for a bottle of spa water 'to dilute my blood, which is apt to be too thick'.

His contemporaries trustingly drank the water for 'Debilities'—in which the blood would probably be too thin.

'INTERMITTENTS' AND 'REPLETION'

The next fifty years saw the steady commercialization of spa therapy. At Scarborough, the local guide-books and medical men became increasingly 'brochure-minded', and there was soon no conceivable ailment which would not benefit from Scarborough sea- or spa-water. Our forebears were no less suggestible than ourselves (Dr. George Cheyne, a Bath physician who died there in 1743, wrote a book proving that hypochondriasis was the 'English Malady'; his other achievement was to weigh 32 stones [200 kg.]) and Scarborough and its invalids gained much benefit. Smollett knew Scarborough well, and made his irritable, middle-aged Matthew Bramble attend for constipation and gout. By 1811, pyrexial and distended sufferers were gulping down the spa water for 'Intermittents, obstructions, nervous or putrid fever' and, unashamedly, for 'Repletion', on the recommendation of local guide-books.

As Dr. Thomas Short had previously announced that Scarborough spa water 'can give a pretty brisk priapism', the literature included in its catalogue of complaints 'Sterility . . . and Particular Weaknesses', thus anticipating the modern 'small-ad.' which whispers, 'Men! Why be old at Forty?'

An interesting but improbable effect of spa waters is mentioned in a pontification against 'Cosmetickes . . . an odious baneful custom . . .' in the 'New Scarborough Guide' for 1797. As the author is believed to have spent several years in Scarborough gaol, this is Satan rebuking sin with a vengeance. Females are warned that bismuth and 'Spanish white' used in face-powders may react with the sulphur in the spa water and turn the complexion black.

Any inconvenient sequelæ, however, were more expediently associated with rival resorts, such as Harrogate.

'Invalids who go to Harrogate without advice', wrote Dr. Breary in his 'Medical Guide to Scarborough' (1855), implying that these were the only circumstances under which any invalid would go to Harrogate, 'and feel grieved after a course of the waters to find that their stomach is in an irritable condition . . . by going afterwards to Scarborough they will find means to counteract that unpleasant result'.

The means of counteraction included his 'Scarborough Salts', retailing at two shillings per bottle and not genuine without his signature on the label.

THE ROUTINE OF SEA-BATHING

'All sunk beneath the wave,
Fast by their native shore'. Cowper.

The accepted ruling was that sea-bathing and drinking the spa waters should be done fasting. Tide permitting, the visitors bathed and then walked across the sands to the spa well.

However, the 'more delicate cases bathe nearer noon . . . and should immediately be wiped dry . . . and put on a flannel-gown . . . and may require friction with dry flannels all over' (Hinderwell's 'History', 1811).

Smollett's character, Matthew Bramble, bathed at 6 a.m., 'the wind northerly and the weather hazy', and 'the water proved so chill that I could not help sobbing and bawling out'. His faithful valet decided his master was drowning and dragged him ashore by one ear 'bellowing with pain onto the dry beach' before an interested crowd.

Males bathed nude and, cold no longer, the embarrassed Bramble fled back into the sea and took shelter in his bathing-machine. He complained: 'I have had a burning heat and a strange buzzing noise in that ear ever since. . . .'

The classical four-wheeled bathing-machines appear in early prints of Scarborough (fig. 1), and in 1797 the 'New Scarborough Guide' announced 'forty good roomy machines' under the care of three widows, who provided bathing-dresses and caps of oiled silk for the ladies. Each bathe cost one shilling and, complained a visitor, 'a gratuity nearly equal to the charge'. The machine was drawn into deep water, when a canvas hood or 'tilt' could be dropped over the seaward end to afford private entry into the water. (George III, bathing at Weymouth, had a band of fiddlers concealed in a neighbouring machine, and entered the water to the invocation 'God Save the King', as though he was a ship undergoing launching. Should the sea prove chilly, the music would also mask any royal cries of anguish.)

A typical Scarborough sea-bathing attendant was caricatured by Rowlandson, in 1811, as 'Mrs. Ducker', a powerful and morose lady riding upon a dolphin and wearing an Empire-style blue 'flannel-gown' and mob-cap.

The effects of sea-bathing upon the Georgian constitution were profound:—

'When a healthy person plunges into the sea, he feels a considerable shock or chill . . . a sobbing succeeds, the skin is contracted and feels rough to the hand, a cracking noise is heard, followed by a ringing or whizzing in the ears; on quitting the water, tears sometimes fill the eyes . . . and many persons experience a little shudder . . . and later a general glow succeeds and the spirits are raised'.

The description concludes ominously—when one remembers the formidable Mrs. Ducker—'The guides powerfully recommend three immersions'.

The more effete could attend for hydrotherapy at one of several indoor baths, in which the routine was presumably based upon that already established in older spas.

INDOOR BATHING

Smollett gave a gruesome account of a Harrogate bath as 'a dark hole on the ground floor, where the tub smoaked and stink like the pot of Acheron' and in which he nearly suffocated. The 'tubs' were long, narrow contraptions so suggesting coffins that an occupant must have felt he was rehearsing for his own wake. Interior details of Scarborough baths are lacking until the beginning of the 19th century. Then the indoor baths were erected by, or named after, local medical men and contemporary guidebooks were suitably fulsome:—

'Comfort and elegance . . . with baths in wood or marble adapted for plunging . . . every variety of temperature . . . also Shower-baths and Warm Pumping . . . the apparatus on the most philosophical principles'.

Not to be outdone, the nearby seaside village of Filey proclaimed:—

'A Warm Bath may be procured by applying at the house of Mr. Munro, Surgeon, who is possessed of a portable one manufactured of Tin, on an improved construction, which can be lent out, or persons may be accommodated with it at Mr. Munro's house'.

The warm baths were taken two or three times a week. 'Never after plentiful Eating or Drinking; Bleed and Purge before and after; and afterwards to bed between blankets . . .' was Dr. Shaw's sensible advice in his 'Treatise on Spaw Waters' (1734).

DRINKING THE WATERS

There was an appropriate ritual governing the drinking of spa waters, a course of which lasted up to six weeks. Dr. Thomas Short wrote in 1734:—

'Do not get overtired by the journey to Scarborough . . . and avoid spirituous liquors. On arrival, wait two or three days before beginning the waters, to let disturbed Secretions and Evacuations return to their natural regular Channel. If costive, take a laxative such as Rhubarb to clear the Passages and make Room and Way for the Water'.

Thereafter, Dr. Short suggested 1 to 1½ pints daily of 'Spaw Water', increasing gradually up to four pints per day. He warned against over-indulgence, which may 'throw the whole Economy into a Deluge' and even have a 'fatal Consequence'. Ideally the drinker should take one pint every hour with gentle exercise such as riding in a 'Chaise or Chariot' between doses. Considering that some of Dr. Short's contemporaries elsewhere were ordering up to twenty pints per daily session, the Scarborough toppers got off lightly.

They got off even more lightly under Dr. Belcombe, a Scarborough physician 'of genius, candour, industry and experience' ('Scarborough Guide' for 1796) who 'with great liberality . . . does not see any necessity for taking preparatives'. The catalogue of Dr. Belcombe's qualities should certainly have included tact.

Other victims drank at dinner a glass of spa water mixed with wine, whilst more submissive sufferers added 'Scarborough Salts', or even drank a mixture of equal parts of sea- and spa-water, 'and I believe that one [glass] of each was generally considered sufficient', said the 'Scarborough Medical Guide' of 1855—a statement not hard to believe.

EPILOGUE

It appears extraordinary how, nauseated, purged and bled, half-frozen and half-drowned in the sea, and parboiled and half-suffocated in the baths, people returned year after year to undergo a routine which could be as much a test of endurance as a course of treatment, and which, if it did not restore, at least proved the possession of a tough constitution.

CURRENT THERAPEUTICS

CXI.—SPIRAMYCIN

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THE tremendous developments in the isolation and characterization of new antibacterial agents produced by microbes has been well emphasized. The number of active substances which have been isolated give the appearance of being almost geometric with time since the establishment of the usefulness of penicillin. Of these many products, a handful have been of potential value for the prevention and/or treatment of human disease. Among the latter, some have become well established as good or excellent therapeutic agents; others have been found to have serious limitations which have made them of restricted or little use in the therapy of human disease. Still others have had such an insufficient trial that their position is not clearly defined. In addition to the latter, there are agents whose worth is unquestioned but whose position is not clear since the mode of action closely approximates that of one or more of the agents firmly established by successful use. Assessments of value in this situation are often based upon considerations such as availability of other agents and the economic factors in their production. Enthusiasms for and against the use of such agents are therefore apt to be regional and fluctuate with the attitude of practitioners towards the new and previous agents—attitudes which are not without bias originating in advertising. Spiramycin seems to be such an agent. In this article the bias will undoubtedly be that originating from the contemporary situation of antibiotic medicine in the United States.

SOURCE

Spiramycin ('rovamycin') was isolated from a strain of *Streptomyces* named *Streptomyces ambofaciens* which was obtained from their native soil by a group of French scientists (Pinnert-Sindico, 1954). A summary of the method of production, chemical characteristics, pharmacology, antibacterial activity and clinical trials originally performed by these workers was first given in the United States at the Second Annual Antibiotic Symposium in Washington, D.C., in 1954 (Pinnert-Sindico *et al.*, 1954-55).

Streptomyces ambofaciens had previously been reported as producing another antibiotic which was named congocidin (Cosar *et al.*, 1952). This antibiotic, however, is left in the aqueous phase of the glucose corn steep liquor or other media when spiramycin is extracted from the media with an organic solvent such as methyl isobutyl ketone or amyl acetate at pH 9. Spiramycin is then prepared by further extraction with aqueous acid, re-

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alkalinized and re-extracted with benzene or ether which is evaporated in a vacuum leaving the powdered antibiotic. Separation by such methods as chromatography reveals that the material so prepared has three active

	Number of isolates	Minimal inhibitory concentrations		
		Phage	Effective against	
			50% of isolates	90% of isolates
<i>Micrococcus pyogenes</i> var. <i>aureus</i>	688	< 1 to > 100	< 3.9	< 10
<i>Gaffkya tetragena</i>	1	0.8		
<i>Sarcina lutea</i>	1	0.8		
<i>Streptococcus faecalis</i>	12	1.0 to > 250	2.0	3.0
<i>Streptococcus viridans</i>	1	1.4		
<i>Streptococcus pyogenes</i>	14	0.12 to 2.0	0.5	1.0
<i>Diplococcus pneumoniae</i>	13	0.2 to 0.3	0.3	0.3
<i>Bacillus subtilis</i>	1	3.0		
<i>Corynebacterium pseudodiphtheriticum</i>	1	3.0		
<i>Neisseria catarrhalis</i>	1	10.0		
<i>Escherichia coli</i>	1	31.0		
<i>Klebsiella pneumoniae</i>	1	33.0		
<i>Aerobacter aerogenes</i>	1	31.1		
<i>Proteus vulgaris</i>	1	> 1500		
<i>Pseudomonas pyocyanea</i>	2	> 1500		
" sp.	1	3.9		
<i>Mycobacterium</i> sp.	1	23.0		

TABLE I.—Minimal inhibitory concentration of spiramycin in mcg./ml. for various micro-organisms.

components, two of which are very similar. The physical and chemical properties suggest that the compound is in the erythromycin-carbomycin group (Pinnert-Sindico *et al.*, 1954-55).

ANTIBACTERIAL ACTIVITY

The antibacterial activity of spiramycin is somewhat similar to that of the related antibiotics. It is most effective against gram-positive organisms, with some activity against mycobacteria, gram-negative bacteria, and rickettsia. In table I it is seen that among the gram-positive cocci, the pneumococci are the most sensitive and *Streptococcus pyogenes* the next. Other species of streptococci, *Micrococcus pyogenes* and the gram-positive rods are generally sensitive but the results are less uniform. Because of their importance in that they are resistant to many of the other antibiotics, staphylococci have been studied most extensively. In table II are recorded the sensitivities of 1,089 isolates from two hospitals at a time before and following the use of this antibiotic in the hospitals. It is evident that highly resistant strains were not frequent and that there was only a rough correlation between erythromycin and spiramycin resistance. Some cross-resistance between erythromycin and carbomycin on the one hand and spiramycin on the

other has been reported by Pinnert-Sindico and his colleagues (1954-55) and Ravina *et al.* (1955-56).

Jones and his co-workers (1956) have shown that four strains of staphylococci exposed *in vitro* to erythromycin, carbomycin, oleandomycin, or streptogramin showed a rapid increase in resistance to spiramycin. High degrees of spiramycin resistance were reached in 3 to 6, 10 to 15, 3 to 6, and 15 to 20 subcultures respectively. Conversely, when these strains were

		M.I.C. of spiramycin (mcg./ml.)				
		< 1	1 to 10	10.1 to 100	> 100	Total
M.I.C. of erythromycin (mcg./ml.)	< 1	11	777	40	0	828
	1 to 10	0	23	20	2	45
	10.1 to 100	0	17	13	4	34
	> 100	0	151	9	22	182
	Total	11	968	82	28	1,089

TABLE II.—Minimal inhibitory concentrations (M.I.C.) of spiramycin compared with those of erythromycin on 1,089 isolates of *Micrococcus pyogenes* var. *aureus*.

grown in the presence of spiramycin within ten subcultures, they became highly resistant to each of the other agents except streptogramin, as well as resistant to spiramycin itself.

In clinical trials two mechanisms have been demonstrated as contributing to the occurrence of spiramycin-resistant staphylococci. We (Lepper *et al.*, 1955-56) were able to demonstrate an increase of the minimal inhibitory concentrations of spiramycin for the organisms isolated serially from the patient in six instances. In the three instances among these, on which the test was done, serial isolates were shown to be of the same phage type. These six patients from whom the isolates were made were among 27 treated with the drug. In other studies we have been able to show (Lepper *et al.*, 1956-57) that extensive use of spiramycin allowed the rapid accumulation of the pre-existing resistant strains to a dominant place in the hospital community. Moreover, the concurrent use of novobiocin did not prevent this accumulation. The strains which accumulated also showed an increased frequency of resistance to erythromycin and oleandomycin, even though neither of these drugs was used in the hospital.

TOXICITY

The toxicity of the drug is low. The LD_{50} in mice is 150 to 250 mg./kg. for the intravenous route, 10 times as high for the intramuscular route, and 20 times as high for the oral route. On the other hand, 0.5 mg. daily gave protection for ten days to more than 50 per cent. of mice (each weighing 20 g.) infected with pneumococci. On a weight basis it is more effective than either carbomycin or erythromycin in the mouse pneumococcal infec-

tion. This somewhat greater effect *in vivo*, in spite of a lesser effect *in vitro*, may be related to the favourable distribution of the drug which occurs into the tissues, particularly the lungs. Other infections in mice successfully treated have been those induced with hæmolytic streptococci and staphylococci.

BLOOD LEVELS AND DOSAGE

The serum concentrations of the drug following the oral administration of 75 mg./kg./24 hours, or a single 20-mg./kg. dose, are not consistent enough to be relied upon. Consequently, 100 mg./kg./24 hours or more is needed in children. In adults, 3 g. a day may not be sufficient for some infections and a regimen such as that used by Hudson *et al.* (1956), of a 2-g. initial dose and 4 g. a day thereafter seems advisable.

CLINICAL RESULTS

The results obtained in the treatment of several groups of infections which would be likely to respond to a sufficient dose given orally are shown in table III. If one omits the infections caused by *Hæmophilus* and *Klebsiella*, in which the drug would not be expected to exert much effect, and staphylococcal infections, which are a particular problem, a difference is seen between the results obtained with 3 g./24 hours or less in adults or 75 mg./kg./24 hours or less in children, and those obtained with larger doses. Thus, among 87 patients who received the lower dose, seven had a fair response and nine had a poor one including one death. On the other hand, among 42 patients receiving the higher doses, and one the lower dose plus local therapy, there were only two who did not do well. As might have been expected from the *in vitro* work, pneumococcal infections were most responsive and other lung infections also responded well, perhaps because of good penetration by the drug into the lung tissue. Streptococcal infections responded well when the larger doses were used. Because of the problem of resistant strains, staphylococcal infections did not do well. The patients with milder skin and soft tissue infections responded well but those with deep-seated and severe systemic infections fared poorly even when large doses were used. Thus, in this crucial area where the drug was most needed, it gave the poorest results.

When the results of treatment were measured in terms of eradication of pathogenic microbes from the patient, the results were similar to those arrived at by clinical criteria (Lepper *et al.*, 1955-56). Pneumococci were uniformly eradicated even by low doses, but only larger doses succeeded in removing beta-hæmolytic streptococci. The staphylococcus was demonstrable in well over 50 per cent. of the patients after spiramycin had been administered for 5 to 7 days, and the strains isolated from the follow-up cultures were often resistant. *Klebsiella* and *H. influenzae* also were not eradicated.

In patients with pneumococcal and streptococcal infections the results obtained compared favourably with those obtained in the same hospital with penicillin and tetracycline. The rapidity of febrile and symptomatic

Disease	Dose*	Response		
		Good	Fair	Poor
Caused by hæmolytic streptococcus	Low	21	2	5
	High	15	0	0
Pneumococcal pneumonia	Low	14	2	0
	High	15	1	1
Pneumococcal otitis media	Low	5	0	1
Pneumococcal carrier state	Low	9	0	0
Staphylococcal infection	Low	17	9	3
	High	1	0	3
Enterococcal endocarditis	High	1	0	0
Enterococcal pyelonephritis	Low	0	1	1
Otitis media caused by <i>H. influenzae</i>	Low	0	2	1
Pneumonia caused by <i>Klebsiella</i>	High	0	0	1†
Lung abscess	Low	1	0	0
Pneumonia of unknown origin	Low	15	1	1†
	High	11	0	0
Empyema of unknown origin	Low + Local	1	0	0
Pharyngitis of unknown origin	Low	2	0	0
Otitis media of unknown origin	Low	4	1	2

*Low dose = 3 g. or less a day in an adult; 75 mg./kg./24 hours or less in a child.

†Patient died.

TABLE III.—Results obtained with spiramycin administered orally to patients with various infections.

response was essentially the same. The drug has also been used successfully in gonorrhœa (Pinnert-Sindico *et al.*, 1954-55) and has been suggested for use in rickettsia and treponemal disease (Ravina *et al.*, 1955-56).

Toxicity.—There is general agreement that toxicity is low. Only the bitter taste if the tablet disintegrated in the mouth (Hudson *et al.*, 1956) and loose stools have been mentioned (Hudson *et al.*, 1956; Lepper *et al.*, 1955-56; Ravina *et al.*, 1955-56). The latter generally consisted of increase in number and looseness of stools but frank diarrhœa was rare. In the three studies mentioned, minor stool abnormalities occurred in about 10 per cent.

of the patients. No reports have appeared of any toxic effect on the liver, kidneys, or bone marrow.

DISCUSSION AND CONCLUSIONS

When a new antibacterial agent is introduced, it is always hoped that it will have a reasonable expectation of proving successful in the treatment of patients in whom the already existing agents have failed. Because most strains of a staphylococcus resistant to erythromycin were not resistant to spiramycin, it was felt that this new antibiotic might have been such a drug. From the *in vitro* work on blood levels, tissue distribution and minimal inhibitory concentrations, good results were to be expected in pneumococcal infections and streptococcal infections and less consistent results in the case of the staphylococcus. This proved to be the case. On a weight basis, however, the dose needed to treat pneumococcal infections is larger than that used for most of the currently available agents and that for streptococcal infections is still higher. In staphylococcal infections the potential to allow resistant mutants to become predominant while the drug is being used, as well as adverse effects on the environmental accumulation of staphylococci resistant to related compounds as well as to itself, is unfortunate. It is for these reasons that it seems unlikely that spiramycin will have any consistent advantage over erythromycin in the treatment of any infections and it will have the disadvantage of poor absorption and hence a higher dose.

Spiramycin therefore seems to be a satisfactory antibiotic with demonstrated effectiveness. Its pharmacological properties, however, are somewhat unfavourable and there are few patients in whom the drug would be specifically recommended. Since most of these would have serious staphylococcal infections only an occasional favourable result can be anticipated.

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EQUIPPING THE SURGERY

III.—THE SPHYGMOMANOMETER

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No patient has been properly examined medically unless his blood pressure has been taken. Efforts to estimate the blood pressure from the radial pulse are pointless nowadays and the results are likely to be as misleading as attempts to estimate the degree of atheroma throughout the body by assessing the hardness of an inch or so of the right radial artery at the wrist.

The two main points in sphygmomanometry to which attention must be paid, as in using any other instrument, are first the best type of machine for general purposes, and secondly the correct technique of using it. So important is attention to minutiae in taking the blood pressure that in 1939 a joint report was issued by the American Heart Association and the British Cardiac Society, and many of their recommendations have been incorporated in this article.

THE MACHINE

The principle consists of balancing the pressure of the blood in the brachial artery against air pressure as measured from a flat rubber bag contained within an undistensible cuff or arm band. Choice of instrument lies between the aneroid type and the mercurial manometer. If the machine is new and well made either kind is accurate, but if the aneroid machine becomes faulty, and it is apt to do so more often than the mercury one, it may be some time before this inaccuracy is realized. In fact, as it should be calibrated at least once a year against a mercurial instrument, there seems little advantage in using it. There are fewer moving parts to go wrong in the simple mercury manometer.

Any good make of mercurial sphygmomanometer is satisfactory nowadays. My own favourite machine is a well-known American model but it is difficult to obtain in this country, and fortunately recent ones of British manufacture are as reliable. It is poor economy to buy one recording only to 260 mm. Hg, although it must be admitted that the long-term clinical significance of a systolic figure of 260 as opposed to 300 is not really known. Not only is the diastolic figure of more importance prognostically, but of even more importance than the actual figure, of course, is whether the hypertension is of the benign or malignant variety. In addition, the condition of the cerebral and coronary arterial walls, the state of the left ventricular muscle and the amount of damage to the kidneys all play a more important part prognostically than the blood pressure figure itself. In other words, it is hypertensive heart disease which matters, not the hypertension.

The cuff for an average-sized adult should be 5 inches (13 cm.) wide, but

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if the arm is fat, or leg readings are taken round the thigh, a 7- or 8-inch (18 or 20 cm.) cuff should be used or the readings will be too high. For young children the cuff width should be 3 inches (8 cm.), but if this is not available then folding an adult cuff longitudinally serves as well. For infants a cuff width of 2.5 cm. should be used.

TECHNIQUE

The patient must be at rest both physically and mentally, and if he has hurried to the surgery, or if he is over-anxious concerning the result, for example if it is part of an important insurance examination, time must be allowed for the 'casual pressure' being taken to become as 'basal' as possible. For this reason it is good practice to take the reading at the beginning of the examination and again at the end. If the first reading is much higher than the second, however, it may well be that he is a hyperreactor and thus a candidate for sustained hypertension in later year (Hines and Brown, 1933).

Another simple fact that is easily overlooked is the hydrostatic effect of the level of the arm compared with that of the heart. The arm should be supported so that the centre of the cuff is at the level of the root of the aorta opposite the 4th intercostal space. Since insurance-rating statistics are based on minor changes in the systolic and diastolic pressures, errors in the accurate positioning of the arm can lead to unfair loading. Ellis (1951) has shown that if the centre of the cuff is only 7 cm. above the 4th intercostal space the pressure may be 131/80 mm. Hg, whereas if it is 7 cm. lower than the 4th intercostal space it may be 145/94 mm. Hg!

The arm must be bared to the shoulder, and if the sleeve is turned up it should not constrict the upper arm. The lower edge of the cuff should be above the antecubital fossa, and the middle of the rubber bag should overlie the brachial artery, which can be felt pulsating along the inner side of the upper arm. The arm band is folded evenly and closely round the arm, and some cuffs are made with a metal fastener as an aid to this, but this seems an unnecessary elaboration.

Systolic pressure.—The patient is warned that his arm will feel constricted for a few minutes and then the bag is rapidly inflated while the examiner keeps his finger on the radial artery until the pulse disappears. The bag is then slowly deflated and the point at which the radial pulse reappears is noted as this denotes the approximate systolic pressure. The bag is then completely deflated. Once more it is pumped up, this time to about 30 mm. above the systolic pressure as found by palpation. It is then slowly deflated again while auscultation is carried out by means of a stethoscope placed lightly over the brachial artery, which can be localized by palpation in the antecubital fossa. The highest level at which sounds are heard represents the systolic pressure. They are dull thuds and sometimes very soft at first so that very careful auscultation is needed. If the bag is let down slowly at this stage one of the most important of the bedside signs of left ventricular failure will be detected if present, namely, pulsus alternans.

Korotkow's phases.—As the pressure is lowered the phase of the dull thudding sounds (phase I) soon gives way to sounds more murmurish in character (phase II). These murmurs are then replaced by sharper 'banging' sounds (phase III) which are apt suddenly to become muffled again (phase IV). As the pressure is still further reduced by a few millimetres, usually about five, the muffled sounds disappear altogether and no sounds can be heard. This final silence constitutes the fifth phase, but occasionally it is absent, particularly in conditions associated with vasodilatation such as aortic incompetence, and sounds may then be heard down to zero.

Diastolic pressure.—The diastolic pressure should always be taken by auscultation. In Great Britain and Ireland the diastolic figure is taken as the point where the sharp sounds suddenly become dull, namely at the beginning of the fourth phase, and this is known as the fourth point. In Canada and the United States, however, the diastolic figure is taken at the fifth point where all sound just disappears, namely at the beginning of the fifth phase. It is a fact that the greatest number of actuarial life insurance statistics are based on this fifth point and it is therefore the practice of some Canadian insurance companies operating in this country to request both fourth and fifth point readings, and if the fifth point is not given by the examiner they subtract 5 mm. from his fourth point reading.

Intra-arterial pressure tracings show that the fifth point is, in fact, nearer the true diastolic pressure than the fourth point (Steele, 1942), and there seems to be no good reason for adhering to the fourth point, particularly as it is often easier to determine when all sound disappears than when one type of sound changes to another, especially if the change is not abrupt.

The reason for first checking the systolic pressure by palpation is to avoid falling into the auscultatory silent gap, which is usually associated with hypertension. Otherwise, if the pressure in the bag has not been raised above the actual systolic pressure, and the bag is let down while listening in the silent auscultatory gap, then the first sound to be heard below the silence will be erroneously regarded as representing the systolic figure. Even so, the absence of an ensuing four clear phases should raise suspicion. Another source of slight error is the taking in rapid succession of several readings. In some people this causes both systolic and diastolic figures to drop a little, presumably due to reduction in tone of the arterial wall.

After taking the blood pressure on the right arm the left pulse should be compared with the right, and if any difference is present the blood pressure should be recorded also from the left arm.

In auricular fibrillation the reading must, of necessity, be approximate, and both systolic and diastolic figures are taken when the majority of beats appear (systolic) or become muffled (4th phase) or disappear (5th phase).

NORMAL BLOOD PRESSURE

As the blood pressure normally falls a few millimetres with inspiration, for clinical purposes it may be recorded to the nearest multiple of five, although

this practice is apt to annoy life insurance underwriters and actuaries! For that matter, I have long since given up trying to get agreement as to what constitutes the normal range of blood pressure between life insurance medical officers, cardiologists and obstetricians.

An adult reclining and rested should have a systolic pressure of not more than 150 mm. Hg, and a diastolic pressure of not more than 90 mm. Hg. Recently, however, attempts have been made to accept higher figures as normal, both systolic and diastolic, and particularly at older ages (Master *et al.*, 1950). It is probable that a diastolic figure of 95, or even 100, in a person over 50, particularly a woman, can often be normal. More attention should be paid to the diastolic figure than the systolic, and to repeated rather than single readings. The diastolic pressure is not only more stable but is more indicative of the increase in peripheral resistance, which is the fundamental feature of hypertensive disease. It also represents the constant load to which the vascular walls are being submitted.

In children the pressure is lower: according to Judson and Nicholson (1914), between the ages of 3 and 9 it averages 90/60 mm. Hg, between 10 and 12, 95 to 100/60 to 65, and between 13 and 15, 105/65.

It is usual to take the pressure in the right arm. If it is found to be raised it should be routine practice to take it in the left arm also and to palpate the femoral pulse. Normally, the femoral pulse can be felt a fraction before the radial. If the femoral pulse is diminished or delayed coarctation of the aorta is unmasked. Slight disparity between the readings taken from each arm may, however, occur in health. If any difference in pressure is present it is usually the right arm which gives the higher reading, but according to Amsterdam and Amsterdam (1943) this rarely exceeds 5 mm. Hg.

It is often stated that the pressure in the legs is 20 to 40 mm. Hg higher than in the arms, but intra-arterial records do not support this, and if the correct 7 to 8 inch wide cuff is used on the thigh the blood pressure in the legs will be found to be similar to that in the arms.

Standing blood pressure.—Now that potent hypotensive drugs are being used more frequently, and postural hypotension can be easily induced by them, it is becoming increasingly common practice to record the blood pressure with the patient standing. According to Currens (1948), in two-thirds of normal subjects the systolic pressure is not appreciably altered, but in one-third it falls by 10 to 15 mm. Hg. The diastolic pressure rises about 5 mm. in one-half, and in the remainder it is mostly unaffected, dropping about 5 mm. in 12 per cent.

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REVISION CORNER

THE TREATMENT OF STATUS EPILEPTICUS IN CHILDREN

OTHER than hæmorrhage and asphyxia, relatively few conditions demand immediate treatment, allowing no time for temporization, broad reflective thought or even quick reference to some 'Vade Mecum'. Status epilepticus is such a disease for, while it lasts, mentality suffers, and life itself is in danger. Infants especially are subject to a high mortality rate, and it is wise to have a therapeutic regime ready to put into action immediately. A great many different treatments are available, mainly involving various sedative drugs, although some people favour lumbar puncture which is hardly applicable outside hospital. This article will confine itself to measures either easily, or at least possibly, manageable at home.

THE MUSTARD BATH

Status epilepticus consists of a series of major convulsions running into each other; separated, if at all, by periods of coma. Thus there is an unconscious child with continuous clonic muscular contractions, usually involving the whole body. Conjugate deviation of the eyes is common, but unless tonic contractions are marked there is unlikely to be much cyanosis. The duration may be from only a few minutes to several hours or even days. This clinical picture is so easily recognized that any doctor should be prepared to diagnose it, at least tentatively, from a description over the telephone, and it is at this point that the old treatment of a mustard bath should be remembered. The mother can carry it out in the interval before the doctor arrives; even if the proportion of successful cases is small, it gives her something to do at a time when it appears that her child may die for want of treatment. A mustard bath is now so rarely used that it may be permissible to remind practitioners how it is made. To each two gallons (9 litres) of water at body temperature, add half a teacupful of mustard.

Assuming that on arrival at the house, the practitioner finds the child convulsing, three things must be done in the following order:—

- (1) Immediate suppression of the convulsions.
- (2) Maintenance treatment to prevent recurrence.
- (3) Exclusion of a primary disease which, though causing the convulsions, requires separate treatment of its own.

IMMEDIATE SUPPRESSION OF CONVULSIONS

This is best and most certainly achieved by inducing *light chloroform anaesthesia*. It may be wondered whether a substance known to produce

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both liver atrophy and vagal inhibition is the drug of choice, when the same effect can be obtained with ether or ethyl chloride; but the advantages of chloroform more than outweigh any possible contraindications, which in a fairly long experience I, at least, have never encountered. Ether anaesthesia will require a 'drop bottle' and a mask, and in addition it should not be used in the presence of an open fire. In the British climate this may well exclude its use for eight months in the year! Ethyl chloride also requires a mask, and tends to produce tonic spasm; in addition, it is difficult to maintain a satisfactory level of anaesthesia unless one is a skilled anaesthetist.

Chloroform, apart from its non-inflammability, really requires no apparatus at all. Of course a drop bottle and mask are useful if the practitioner happens to carry these things around with him on all occasions, but they are not really necessary. All that is required is to remove the cork from a bottle of chloroform; put the index finger over the opening; take a corner of the sheet, a clean handkerchief or any other piece of material available and pour some chloroform on to it. If a small quantity comes out, the sheet is held near the child's face, but if by chance rather a lot pours out then it is held farther away. Such is the potency of the drug that in either case the desired state of anaesthesia is rapidly induced, and it should be maintained for approximately five minutes. Although anaesthesia is a certain method of stopping convulsions, it is unfortunate that in most cases they will return as the anaesthetic is excreted. It is therefore necessary to proceed to the second stage of treatment which is maintenance treatment.

MAINTENANCE TREATMENT

As the child is quite unconscious, no drugs can be given by mouth unless a stomach tube is passed. This means that it is only really applicable to cases in hospital. As a matter of fact this method is indicated in but a few infants, who respond to chloral hydrate better than any other drug. As a general routine, an intramuscular injection is the method of choice, and a rapidly acting drug is required since it must take effect before the anaesthetic has worn off, or further chloroform will have to be given. The drug which best fulfils these requisites is *paraldehyde* which, although only effective for an hour or so, produces its effect within minutes of being injected, and will generally control the convulsions before the chloroform has been excreted. As in all drugs used in this condition, it is useless trying small doses since they will have to be repeated in further small amounts until one gets the cumulative toxic effects of a large dose without having managed to control the convulsions. Intramuscular paraldehyde should be given in a dose ranging from 1 to 1.5 ml. for an infant; 3 ml. at the age of five and 8 ml. at the age of ten. Further maintenance control can be achieved with paraldehyde but, owing to its short action, the injections are likely to require repeating at two-hourly intervals.

As a general rule it is better to follow up the first injection of paraldehyde

with injections of *soluble phenobarbitone*. Thus, as soon as there are signs that the effect of the paraldehyde is wearing off, soluble phenobarbitone should be injected intramuscularly. The dose is $\frac{3}{4}$ grain (50 mg.) for a child up to a year; $1\frac{1}{2}$ grains (0.1 g.) up to four years; $1\frac{3}{4}$ grains (0.11 g.) up to seven years, and 2 grains (0.12 g.) for older children. This will usually control the convulsions for from four to six hours, when further doses may be given.

In a small proportion of cases phenobarbitone does not act for such long periods, and these cases usually continue convulsing for several days unless kept heavily sedated. Should such a case be encountered, the most useful drug is *bromethol*. It is unfortunate that owing to its abandonment by anaesthetists the drug is not easily obtained; it is also a little difficult to prepare and has to be administered per rectum. The latter is no real problem in an unconscious child if the fluid is run in slowly, the buttocks are raised and finally strapped as the tube is withdrawn. In the type of case described there is no other drug which will give adequate control with a six- to ten-hourly administration. The dose is 0.09 g. per kg. body weight.

It can thus be seen that the treatment of status epilepticus is simply the control of convulsions by heavy sedation, and this must be continued for as long as is required. This point is determined by observing the patient after each therapeutic dose. If in due course the convulsions show signs of recurring, more treatment is required, but should nothing happen no further drugs are given. When the child finally stops convulsing without treatment, consciousness may return and all is well, but this is by no means the rule. Some children remain in coma for days before recovering consciousness, and these cases will have to be fed by stomach tube during this period. Others on recovery are found to be grossly mentally altered; blind or paralysed with a hemi- or di-plegia. Fortunately these dramatic symptoms are rarely permanent and usually disappear spontaneously after a period of time which may run into weeks.

EXCLUSION OF UNDERLYING PRIMARY DISEASE

Whilst the initial treatment for all cases of status epilepticus is the same, it must be remembered that, although idiopathic epilepsy is the underlying cause in most children, some of them may have another primary disease which requires a separate and different treatment of its own. Two examples would be meningitis and chronic renal disease. Therefore after stage one treatment has been completed and stage two begun, it is necessary to make a complete examination of the child. This is not a particularly easy procedure with an unconscious child, but it is not within the scope of this article to deal with the differential diagnosis. One point must be mentioned, and that is the presence of fever. Practically all cases of status epilepticus are pyrexial, due to the heat generated by the intense muscular activity, and if the convulsions are not controlled, death may ensue from hyperpyrexia.

CONCLUSION

Finally it may be said that status epilepticus is an unpleasant and dangerous condition from which to suffer, and that treatment must be planned, intensive, and carried out with determination and courage if any success is to be achieved.

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CEREBROSPINAL FLUID IN HEALTH AND DISEASE

THE cerebrospinal fluid is formed by the choroid plexuses, but whether the mechanism of its production is one of secretion or filtration is still controversial. Sweet, using radioactive isotopes and heavy water, has studied the ionic exchanges of the blood and the cerebrospinal fluid, and considers that there is evidence that the fluid is secreted by the choroid plexuses but that in addition there is an ultra-filtration into the general subarachnoid space.

NORMAL CEREBROSPINAL FLUID

The fluid is clear and colourless and is at a pressure of 60 to 150 mm. of H_2O , when measured with the patient relaxed in a horizontal position.

Constituents.—Cells up to 3 lymphocytes per c.mm. Protein up to 30 mg. per 100 ml. Globulin (Nonne-Apelt reaction) negative. Chlorides: 725 to 750 mg. per 100 ml. Sugar: 45 to 70 mg. per 100 ml.

The protein content consists chiefly of albumin and shows an increase in quantity in the later age-groups, when values up to 60 mg. per 100 ml. may be regarded as normal.

The Queckenstedt test.—Compression of the jugular veins produces a rise in cerebrospinal-fluid pressure, followed by a fall on relaxation. These changes are transmitted to the lumbar sac in the healthy individual and are measured on a manometer.

INFECTIONS OF THE NERVOUS SYSTEM

Pyogenic meningitis.—The degree of abnormality may be slight in an early stage of the infection but usually the fluid is under pressure, is turbid, and contains several thousand polymorphs per c.mm. The protein is increased with a positive globulin, the chloride is reduced to 650 mg. per 100 ml. and the sugar is greatly reduced or absent. Organisms can usually be seen in the direct smear and may be grown on culture.

Tuberculous meningitis.—The pressure is increased and the fluid is opalescent with a fibrin web. There is a moderate lymphocytic pleocytosis with a proportion of polymorphs. The protein content is over 100 mg. per 100 ml., with a positive globulin. The chloride is reduced to 600 mg. per

100 ml. but it should be remembered that this degree of reduction is not invariably present. The sugar is decreased to 20 to 35 mg. per 100 ml. The blood/C.S.F. bromide ratio is used to distinguish between virus infections and tuberculous meningitis, as in the latter the permeability of the blood/C.S.F. barrier to bromide is increased. The tubercle bacillus may be found in the stained film of the centrifuged deposit, and the diagnosis later confirmed by culture and guinea-pig inoculation.

Virus meningitis.—The pressure is usually slightly increased, the fluid is clear, and there is a lymphocytic pleocytosis, with occasional polymorphs in severe infections. An increase of protein up to 150 mg. per 100 ml. may be present. Rarely, the chloride shows a slight increase, but the sugar is normal.

Poliomyelitis.—The fluid is abnormal in 90 per cent. of cases of poliomyelitis. The maximal pleocytosis of up to several hundred cells, including some polymorphs, occurs in the pre-paralytic period; in the second week the number of cells falls but is replaced by a marked increase of protein which may persist for some weeks. The chloride and sugar content are within normal limits.

Encephalomyelitis.—The post-infective form following the acute exanthemata may cause increased pressure of the cerebrospinal fluid, and minor changes in the cell count. The protein and chloride content are normal. Encephalomyelitis considered to be of virus origin is rare in this country but may be associated with an increase of cells and protein in the cerebrospinal fluid.

Cerebral abscess.—A pleocytosis of about 30 cells per c.mm. is usual, which is predominantly lymphocytic but may contain a few polymorphs. The protein content is increased but the chlorides and sugar are normal. The pressure rises with increasing œdema.

SYPHILIS

The cerebrospinal fluid may show a lymphocytosis in the primary stage. In the secondary stage a sharp meningeal reaction is not uncommon, with a luetic Lange curve.

Lange's colloidal gold reaction.—Abnormal globulin, present in the cerebrospinal fluid in certain diseases of the nervous system, has the property of precipitating a colloidal solution of gold. The results are recorded in figures from 0 (nought) to 5, indicating the degree of colour change and precipitation with progressive dilutions of the fluid. The paretic curve shows a maximal change in the least dilutions of cerebrospinal fluid, and is found in general paralysis of the insane (G.P.I.), in some cases of disseminated sclerosis, and in subacute inclusion encephalitis. A change in colour in the mid-zone or middle dilutions is known as the luetic curve and occurs in tabes and meningo-vascular syphilis, and occasionally in disseminated sclerosis.

In meningo-vascular syphilis, tabes and G.P.I., there is a lymphocytic pleocytosis with some monocytes, an increase of protein and a positive globulin, the changes being most severe in G.P.I., with the diagnostic changes in the Lange test. The Wassermann reaction is usually positive. Martin has stressed the importance of the return of the cell count to normal in assessing the efficacy of treatment.

DISSEMINATED SCLEROSIS

Some abnormality is present in 70 per cent. of cases. Usually there is a slight lymphocytic pleocytosis with an increase of protein and a positive globulin. The Lange test is abnormal in about 40 to 50 per cent. of cases and typically shows a paretic, or sometimes a mid-zone, curve.

CEREBRAL TUMOUR AND SPINAL COMPRESSION

Cerebral tumour.—Examination of the cerebrospinal fluid is of most value in suspected cases of acoustic nerve tumour or meningioma, when the protein is likely to be increased. Secondary deposits may cause increase of protein and malignant cells may be detected. Lumbar puncture is dangerous in the presence of papillædema, and if raised intracranial tension is suspected, expert advice should be sought, as contrast radiography is usually indicated to localize the lesion.

Spinal compression.—The initial pressure is low and Queckenstedt's test is employed to detect the degree of manometric block; the protein content may be greatly increased. It is usual to undertake myelography when compression is suspected on clinical grounds, rather than to wait for the development of complete spinal block.

CEREBROVASCULAR DISORDERS

The findings in *subarachnoid hæmorrhage* have recently been discussed. Xanthochromia may be present as early as four hours after the hæmorrhage and persists for as long as five weeks. The blood is evenly mixed in all three tubes of cerebrospinal fluid withdrawn and there is no clot. The appearance of a lymphocytosis is not uncommon in subarachnoid hæmorrhage and may lead to diagnostic difficulties if the patient shows a slight pyrexia.

Cerebral arteriosclerosis not uncommonly causes a rise in protein, and there is sometimes a yellow coloration in the cerebrospinal fluid.

If a *vascular accident* has occurred, hæmorrhagic or thrombotic, some red cells may be expected.

BARBITURATE POISONING

Examination of the cerebrospinal fluid for barbiturates is an important investigation if barbiturate intoxication is suspected.

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NOTES AND QUERIES

Tetracycline in Chronic Bronchitis

QUERY.—In the treatment of patients who suffer from chronic bronchitis with frequent superimposed bouts of acute bronchitis, do you consider that there is a place for continuous antibiotic administration as a preventative; if so, which antibiotic (and in what dosage) do you consider to be the safest and most effective?

REPLY.—In the treatment of chronic bronchitis, the administration of antibiotics is related to pus in the sputum. The aim of antibiotics is to render the sputum mucoid and keep it so, or to eliminate it completely, at least for the time being. Consequently, there is often a place for short courses when a purulent sputum exists, and many exacerbations can be cut short by taking a few doses as soon as they threaten.

Continuous antibiotic therapy should be reserved for advanced bronchitis. Often it is effective if taken regularly during the winter months. Only severe and debilitated chronic bronchitis require it all the year round. Personal experience in a series of severe purulent bronchitis suggests that an appropriate antibiotic will give considerable relief in about one-half. The others consist largely of those who are troubled with diarrhoea and a smaller number who did not respond to the drug.

As the most important organism in chronic bronchitis is *H. influenzae*, an antibiotic must be selected which combats this organism. The only one which can be taken by mouth which falls into this category is tetracycline. Tetracycline is preferable to oxytetracycline and chlortetracycline in our hands. The dosage is the least required to keep the sputum mucoid. When the sputum is only moderately purulent, 0.25 g. twice a day will often lead to considerable general improvement and clearing of the sputum. In patients with a grossly purulent sputum, 0.5 g. twice or three times a day, or even more, may be necessary.

Diarrhoea occurs in at least half of all patients having continuous tetracycline therapy. If it is mild, the drug should be withheld for a few days, and then on resumption the diarrhoea is usually less troublesome. More severe diarrhoea can often be controlled by a mixture containing kaolin and morphine.

NEVILLE OSWALD, T.D., M.D., F.R.C.P.

Vaginal Discomfort Following Hysterectomy

QUERY.—I should be grateful for advice on the following case:—

A married woman, aged 52 years, had a total

hysterectomy for adenomyosis of the uterus three months ago. In addition to the uterus, the tubes, ovaries, and also the appendix, were removed. She now complains of dryness in the vagina. I would be glad to know:—

(1) Would there be any effect from applying a hormonal ointment or any other cream to the vaginal walls? If so, which is the best preparation?

(2) Is it all right for her to have coitus?

REPLY.—It is not clear from the question whether the dryness in the vagina complained of began after the operation or if it was present before the operation was performed. It is not a complaint commonly attributable to total hysterectomy with bilateral salpingo-oophorectomy. It would be helpful to know if there is any evidence of menopausal atrophy of the vagina or early changes of kraurosis vulvæ. In view of the patient's age and the fact that both ovaries have been removed, the condition might possibly be due to oestrogen deficiency, and a therapeutic test would be reasonable. A pessary containing 1 mg. of stilbæstrol should be inserted into the vagina each night for six to eight weeks, and the local condition assessed at the end of this period. Coitus should not be harmful unless there is stenosis causing disproportion between the organs. Mere dryness could be overcome by simple lubrication.

ANTHONY PURDIE, M.B., F.R.F.P.S., F.R.C.O.G.

Pregnancy and Hypoparathyroidism

QUERY.—I have a patient aged 36, who is pregnant for the third time. Her last menstrual period was three months ago. She had a normal delivery nine years ago and twins two years ago, one of whom died after premature induction of labour for severe toxæmia.

Nine months ago she had a thyroidectomy performed because of thyrotoxicosis. The parathyroids were seen at operation and were left behind. Nevertheless she suffered from hypoparathyroidism after the operation and has only been free from attacks for the last three months. She is now taking tablets of calcium gluconate, 10 grains (0.6 g.) four times a day. She is not taking any vitamin D preparation.

I am anxious to know what effect, if any, the pregnancy is likely to have on the mother and if the baby's skeletal development is likely to be affected. I presume it would be advisable to ensure that the patient takes calcium tablets throughout the pregnancy?

REPLY.—As the patient has not had any mani-

festations of tetany during the last three months, although not taking any vitamin D, it may be concluded that compensatory hyperplasia of the parathyroid glands has taken place. During pregnancy and lactation the calcium requirements are increased—in the former on account of utilization of calcium by the foetus and in the latter through loss of calcium in the milk. The degree of parathyroid hyperplasia that has occurred may not therefore be sufficient to prevent the recurrence of tetany during pregnancy and lactation. In hypoparathyroidism there is inadequate resorption of calcium from the bones so that the density of the bones tends to be increased: this is the only change that takes place in the maternal and fetal skeletons and is usually not detectable on x-ray examination. (It should be remembered that in hypoparathyroidism the effect on the skeleton is different from the case of tetany arising through inadequate absorption of calcium from the gut: in this latter instance defective absorption leads to a fall in the level of calcium in the blood: this causes increased secretion of parathyroid hormone which removes calcium from the bones, resulting in rarefaction and sometimes, in consequence, deformities and spontaneous fractures.)

The aim of treatment should be to prevent the occurrence of tetany in the mother. The administration of calcium should therefore be continued throughout pregnancy and lactation. Calcium is given as calcium gluconate, in doses of 20 grains (1.3 g.) four times daily. Calciferol should be given in addition, in doses of 50,000 units once or perhaps twice daily to facilitate the absorption of calcium from the gut. Milk should not be taken in excess because of its high phosphorus content, for a high intake of phosphorus tends to lower the blood calcium by impeding the absorption of calcium from the gut through the formation of insoluble calcium phosphates.

A. W. SPENCE, M.D., F.R.C.P.

Asthma Precipitated by Colds

QUERY.—I attend a family of five, all of whom suffer periodically from asthma. The parents' attacks, which are frequent, follow common colds and periods of stress, but do not appear to be due to allergens. The two elder children's attacks invariably follow common colds and now the youngest, a fat young boy of fifteen months, has just had his first attack, associated with a cold and bronchitis. How am I to prevent these children, especially the youngest, from becoming chronic asthmatics? Am I doing right in cutting attacks short with adrenaline injections, as heretofore, or should I use corticotrophin or cortisone, or coryza vaccinations?

REPLY.—Asthma precipitated by colds is best treated by general measures; in older children or adults breathing exercises are often helpful. Any measure which terminates the attacks is justifiable and if this is achieved by adrenaline it should be given. Corticotrophin or cortisone may be of value in association with antibiotics, but should not be used unless simpler methods fail. It is rarely necessary for children. There is no scientific evidence that anti-catarthral vaccines are of value. Most children with asthma of this type improve as they grow older, provided attacks are adequately controlled by antispasmodics, and antibiotics if infection persists. They should be encouraged to lead as normal a life as possible with participation in sports of all kinds. Sensitization to dusty materials may develop and it is wise to keep bedrooms dust free and to avoid feather pillows and so on. The following preparation is often helpful, especially at night:—

Camphorated tincture of opium B.P.	2 minims (0.12 ml.)
Oxymel of squill B.P.C.	5 minims (0.3 ml.)
Ephedrine	$\frac{1}{2}$ grain (8 mg.)
Potassium iodide	1½ grains (100 mg.)
Chloroform water to	60 minims (4 ml.)

This prescription is suitable for the child of fifteen months; doses should be increased for older children.

R. S. BRUCE PEARSON, D.M., F.R.C.P.

Dichlorophen in Tapeworm Infestation

QUERY (from a reader in Malta).—My daughter, aged four years, is suffering from tapeworm infestation (*T. saginata*). I have not used Filum capsules as I have had very poor results in other cases. I tried to use mepacrine but she would not swallow the tablets. Do you know of some other form of treatment? What I am after is a drug in the form of a mixture which is palatable to children.

REPLY.—I would recommend that this child be given dichlorophen ('antiphen', May & Baker). The tablets (0.5 g.) are almost tasteless, and four of them, crushed in sugar or jam, should be given before breakfast. There is no need for any starving or purging, nor are there any side effects other than occasional slight colic and looseness of the bowels. If, after treatment, segments are passed for a period of three months the child can be considered cured. As the dose given is only one-third of the amount used for an adult, the chances of cure are not high, but at least the child will be relieved of the passage of segments for some weeks, and the treatment can always be repeated when segments reappear.

D. R. SEATON, M.B., M.R.C.P., D.T.M.

Cortisone in Thromboangiitis Obliterans

QUERY.—As cortisone is used in the treatment of polyarteritis nodosa, would the same treatment be effective in thromboangiitis obliterans, which is also an inflammatory condition of the peripheral vascular system?

REPLY.—I do not know of any evidence that cortisone is effective in the treatment of thromboangiitis obliterans, nor after an extensive search of the literature does there appear to be any recorded case. It is true that cortisone is of value in the early stages of polyarteritis nodosa and is curative in cases of cranial (temporal) arteritis. There is a slight increase in the liability to venous thrombosis during cortisone therapy, but apart from this there is no reason why cortisone should not be tried in thromboangiitis obliterans provided there are no gangrenous areas.

R. I. S. BAYLISS, M.D., F.R.C.P.

Nocturnal Cramp

DR. HENRY RAVERTY (Bray) writes:—In my experience, after nearly fifty years in general practice, the most effective treatment for nocturnal cramp is the drinking of large amounts of water. Plain water as a remedy for cramp is so simple that it seems silly to many people—but it is not so simple. To drink a pint and a half (850 ml.) of plain water when not thirsty is far from easy—but it does relieve the cramp.

Where I practise, in South Co. Dublin and North Co. Wicklow, we have a water supply of

which we are particularly proud. It is a very soft, acid, peaty water, characterized by low contents of total solids, calcium and bicarbonate. The chloride content (as Cl) is 1.3 parts per 100,000 (expressed as sodium chloride = 2.1 g.p.g.). Whether such a wafer has any particular merit I am not in a position to say.

Antihistamine Preparations

DR. C. ALLAN BIRCH writes: In my article on 'Antihistamine preparations' in the January issue (p. 65) I stated that antihistamine drugs are Schedule IV poisons. There are, however, four such preparations which, so far, have not been included in the Schedule: triprolidine ('actidil', Burroughs Wellcome), meclozine ('ancolan', British Drug Houses), buclizine ('vibazine', Pfizer), and chlorpheniramine ('piriton', Allen & Hanburys).

The statement which I made that only three dispensings of a private prescription can be made is only correct when no instructions about repetitions have been given. The Poisons Rules 1949 (Rule 12(4)) state that it is open to a doctor to order a prescription to be dispensed any number of times. If no intervals are stated the prescription must not be dispensed more often than once in three days. Requests for repetition of National Health Service prescriptions must be on separate forms. It may be added that antihistamine preparations intended for external application and those not containing more than 1% of an antihistamine substance (e.g. eye-drops) can be dispensed free from any statutory restriction.

PRACTICAL NOTES

Treatment of Endometrial Tuberculosis

In a report to a joint subcommittee of the British Tuberculosis Association and the Royal College of Obstetricians and Gynaecologists, A. M. Sutherland (*Tubercle*, February 1957, 38, 46) states that 'the results indicate that chemotherapy should be used in patients with proved endometrial tuberculosis'. Of the 113 patients in the trial, 61 chosen at random were given streptomycin and *p*-aminosalicylic acid (PAS), and the remaining 52 were allocated to an untreated group. Patients in the treated group were given 1 g. of calcium chloride complex of streptomycin daily by intramuscular injection for 84 consecutive days, and 3 g. of PAS (sodium salt) four times daily by mouth for the same period. All patients were ambulant

throughout treatment and remained at work, receiving their treatment either at the outpatient department or under the supervision of their family doctors. In the untreated group no active treatment of any kind was given. Four patients developed toxic manifestations sufficiently severe to cause treatment to be stopped. This is described as 'disturbing; but in no case was there any permanent ill-effect'. In 38 (88%) of the 43 patients in the treated group who were followed for a year from the start of treatment, there was no bacteriological evidence of recurrence. Symptomatic improvement was generally satisfactory: e.g. the seven patients complaining of profuse and irregular menstruation all reported a return to a normal menstrual cycle. Of the 33 patients in the untreated group who were followed for a year, in 25 (76%) the endometrium still showed

bacteriological or histological evidence of tuberculosis. The report concludes: 'Further trials have been in progress in which streptomycin and PAS are being compared with streptomycin and isoniazid and with isoniazid and PAS and different durations of treatment are being contrasted. While the present results are satisfactory in view of the short period of treatment, it is probable that longer periods comparable with those used currently in other forms of tuberculosis will prove even more effective'.

Carcinoma of the Œsophagus

AN analysis of the results in the 314 new patients with carcinoma of the œsophagus treated at the Royal Marsden Hospital between 1936 and 1951 is given by D. W. Smithers (*Annals of the Royal College of Surgeons of England*, January 1957, 20, 36). Of the 65 'untreated' patients 95% died within six months and none survived two years. Of the 20 treated by resection, 60% died within six months and only one survived more than two years. Of the 229 treated by radiotherapy, 52% died within six months and 9% lived for more than two years. Of the entire series, only 10 survived for more than five years: seven of the 198 treated by x-rays, two of the 31 treated by radium, and one of the 20 treated by surgery. The results show that surgery is gaining its successes predominantly in the lower third of the œsophagus where access and reconstruction are easy, and radiotherapy in the upper third where involvement of inaccessible lymph nodes below the diaphragm is least common. For tumours in the middle third, radiotherapy is at present the treatment of choice: 'With the minimum of discomfort, with a stay in hospital of a few weeks (usually most helpful for a starving patient who can then be properly fed and cared for) and with virtually no treatment mortality, the majority of these patients, treated by modern methods, swallow well again until their death. Their total survival time in comfort greatly exceeds that currently secured for the surgical group'. An appeal is made for closer cooperation between surgeons and radiotherapists: 'they have their individual sites of maximum advantage, but competition to the patient's disadvantage is still far too common'. The view is expressed that there is a place for combined treatment in some cases, either by preoperative irradiation or by the use of radioactive gold grain implants.

Antacids

IN a detailed analysis of the effect of a wide range of antacids in 144 patients, most of whom

had peptic ulcers, Pentti Koskinen (*Annals Medicinæ Internæ Fennicæ*, 1956, 45, supplement 25) found that magnesium oxide (0.4 g.) was the most effective of those studied. It acted within fifteen minutes and maintained the reaction of the stomach and duodenum above pH 3.5 for forty-five minutes. Seventy-five minutes after it had been administered the pH was only 3.3, indicating that there was no acid rebound. The neutralization produced by sodium bicarbonate (1.2 g.) was only slightly inferior, and occurred fairly quickly, the maximum pH of the gastric contents (4.3) being reached in thirty minutes. The reaction of the stomach remained above pH 3.5 for an hour. The reaction of the first part of the duodenum dropped slightly below pH 3 after forty-five and sixty minutes. No definite reactive rebound acidity was noted. Sodium carboxymethylcellulose (10.6 g.), 'amberlite XE-58' (2.3 g.), calcium phosphate (2 g.) and magnesium trisilicate (2.2 g.) all produced a slight and even neutralization of the gastric contents (pH = 3). Magnesium carbonate (0.8 g.) produced a rapid and definite neutralization but its effect was transient and there was some secondary rebound acidity. The antacid effect of calcium carbonate (0.8 g.) was not very satisfactory, and aluminium hydroxide (2 g.) and sodium lauryl sulphate (1 g.) had no effect upon gastric acidity.

Cerebrosides and Disseminated Sclerosis

WRITING from the Collip Medical Research Laboratory, University of Western Ontario, R. L. Noble et al. (*Canadian Medical Association Journal*, January 1, 1957, 76, 23) report the preliminary observations in a small group of patients suffering from disseminated sclerosis and who have taken a preparation of fatty acids from beef spinal cord cerebrosides continuously for periods of 7 to 17 months (average 12 months). During the period of treatment none of the patients showed an exacerbation of the disease process or developed new lesions, and in one case an extensor plantar response reverted to normal. The opinion is expressed that the results presented in this paper raise the possibility that the maintenance and function of the myelin sheath of nerves may be dependent on the specific nature of the fatty acid components of the cerebrosides which it contains, and also raise the question of an acquired deficiency of such acids being a causative factor. Because of the natural course of disseminated sclerosis and the number of patients treated, it could prove misleading and erroneous to attempt to draw any conclusions at this time'. On the other hand, it is felt that 'the repetition of these experi-

ments should be considered at centres where large numbers of patients are available, and where a careful follow-up study can be made for the necessarily long periods of time required'. A final warning is given that 'until such studies are made the indiscriminate use of the material described or the implication to patients of a new form of therapy for disseminated sclerosis is quite unwarranted'.

Methyl Phenidate in Narcolepsy

METHYL phenidate ('ritalin') 'appears at this time to be the drug of choice in the treatment of narcolepsy', according to D. D. Daly and R. E. Yoss (*Proceedings of the Staff Meetings of the Mayo Clinic*, November 14, 1956, **31**, 620) as a result of their experience with the drug in 25 cases. The duration of the illness ranged from six months to 44 years, with a median of five years. Thirteen of the patients had cataplexy as well as narcolepsy. The initial dose was usually 20 mg. thrice daily, and patients were asked to increase the dose daily until symptoms were reduced or undesirable side-effects appeared. It was found that the usual daily dose ranged between 60 and 80 mg. An assessment of the results shows that 12 patients obtained an 'excellent' response (i.e. 75% to complete remission), nine obtained a 'good' response (i.e. 50 to 75% remission), two showed a 'minimal' response (i.e. less than 50% improvement), and in one case there was no improvement. Of the 13 patients who also had cataplexy, eight obtained complete control of this, or a definite decrease in the number and severity of attacks. It is reported that every one of the 21 patients who obtained 'excellent' or 'good' results considered methyl phenidate to be superior to any other analeptic used. Side-effects were minimal, and consisted of slight 'nervousness', dryness of the mouth and a tendency to perspire freely. In one instance the drug had to be withdrawn because of a generalized rash. It is stressed that flexibility in dosage to meet the requirements of the individual patient is essential if the best results are to be obtained.

Penicillin V in Pneumonia

PENICILLIN V is 'a drug suitable' for the oral treatment of mild and moderately severe pneumococcal pneumonia, according to R. Austrian and A. L. Winston (*American Journal of the Medical Sciences*, December 1956, **232**, 24). This opinion is based upon their experience with 73 consecutive cases of mild and moderately severe pneumococcal pneumonia admitted to hospital during a period of one year. The dosage was 400,000 units twelve-hourly until the rectal temperature had been

below 99.6° F. (37.5° C.) for seventy-two hours. Bacteriæmia was present in 18 cases, and in no instance did this persist after twenty-four hours' treatment with penicillin V. There were two failures in the series. One of these subsequently responded to intramuscular penicillin G. The other, the only death in the series, was a chronic alcoholic who died suddenly on the day after admission to hospital. No necropsy was performed. Although it was not used in this investigation, it is recommended that in the routine treatment of pneumococcal pneumonia an initial parenteral dose of penicillin G should be given to ensure absorption and to lessen delay in the establishment of an effective concentration of penicillin in the body.

Sodium Gentisate in Acute Rheumatism

ON the basis of a small pilot trial, Captain Gerald Sandler, R.A.M.C. (*Journal of the Royal Army Medical Corps*, January 1957, **103**, 27), reaches the conclusion that 'there certainly appear to be greater advantages associated with the use of sodium gentisate than with either aspirin or sodium salicylate in acute rheumatic fever'. His conclusions are based upon the findings in three patients treated with aspirin (20 grains [1.3 g.] five times daily), three patients treated with sodium salicylate (30 grains [2 g.] five times daily), and three patients treated with sodium gentisate (2 g. five times daily). The average length of time for relief of symptoms was 2 days for sodium gentisate, compared with 5.7 days for sodium salicylate and 4.7 days for aspirin. The average period required for a fall of the erythrocyte sedimentation rate was 2.7 weeks for sodium gentisate, 7 weeks for sodium salicylate, and 5 weeks for aspirin. The average duration of treatment was 6 weeks for sodium gentisate, 12.7 weeks for sodium salicylate, and 7.3 weeks for aspirin. No side-effects were encountered in any of the patients receiving sodium gentisate, but anorexia, vomiting and tinnitus occurred in two of those receiving sodium salicylate and in two of those receiving aspirin.

Epidemic Vomiting

A STUDY of six outbreaks of epidemic vomiting in Exeter has been made by G. P. McLauchlan (*Medical Officer*, January 25, 1957, **97**, 47). Three were school outbreaks, and three family outbreaks. The first school outbreak was in a nursery school, and only nine of the 37 children attending the school were involved. In the second, 78 children, two teachers and three kitchen hands were affected in a school consisting of 300 pupils, aged 7 to 11. Twelve

secondary cases occurred in the homes of affected children during the outbreak. The third was in a residential school for the deaf, and 14 of the 143 pupils were involved. The first family outbreak was a small one, in which a family of father, mother and 11-month-old son were all involved. The second involved two families living next door to each other, and in the third four out of six members of the family were affected.

Of the six outbreaks, only one was in the winter. The pattern of the outbreaks suggested that spread was airborne but, as it is known that the virus is excreted in the faeces, the possibility of the infection being passed in the food cannot be excluded. The incubation period was twenty-four to seventy-two hours. The most common presenting symptom was nausea or vomiting, or both. The onset of vomiting was often abrupt. Diarrhoea occurred in less than a third of the patients. Frontal headache, often quite severe, was complained of by a number of the patients, both adults and children. In none of these outbreaks did any of the patients complain of giddiness. None of the children were severely affected and recovery was rapid after the cessation of symptoms.

Cortisone in Leprosy

'THERE is a definite place for the use of cortisone and corticotrophin in certain acute complications of leprosy and of sulphone therapy', according to W. H. Jopling and R. G. Cochrane (*Leprosy Review*, January 1957, 28, 5). The most important of these is erythema nodosum leprosum, an allergic phenomenon which may occur in lepromatous leprosy during the stage of the disease when the bacilli are becoming granular. A five-day course of cortisone—100 mg.—75 mg.—50 mg.—25 mg.—12.5 mg.—will often prove adequate. Alternatively, a five-day course of ACTH gel may be given—40 mg.—30 mg.—20 mg.—10 mg.—5 mg. Sulphone treatment must be continued throughout, but it may prove desirable to make a reduction in dosage. The fact that sulphone treatment need not be stopped is one of the great advantages of the use of these hormones, and the authors are satisfied that 'early fears of aggravating the underlying leprosy have proved unfounded'. Should the reaction not be controlled by a five-day course, treatment must be continued for as long as required, using the smallest effective daily dose and persevering with sulphone.

For the treatment of iritis, iridocyclitis and scleritis occurring as allergic reactions in lepromatous therapy, the instillation of 1% hydrocortisone acetate or cortisone acetate eye-drops is recommended. For severe or persisting

neuritis occurring during sulphone therapy, the intra-neural injection of 1 to 2 ml. of equal parts of 2% procaine and a suspension of hydrocortisone (25 mg. per ml.) is recommended. For acute sulphone sensitization the following daily dosage schedule is suggested as a basis. Cortisone: 200 mg.—175 mg.—150 mg.—125 mg.—100 mg.—75 mg.—50 mg.—25 mg.—12.5 mg. Alternatively, corresponding doses of corticotrophin, prednisone or prednisolone may be used.

Myxœdema Due to Cobalt

BECAUSE of the 'severe myxœdematous state' that it may produce, J. S. Robey, P. M. Veazey and J. D. Crawford (*New England Journal of Medicine*, November 15, 1956, 255, 955) urge that cobalt should only be used in the treatment of anæmia when there are precise indications for its use. They give details of a severe case of myxœdema in a 17-month-old girl directly attributable to cobalt. This child, who had been found to have a hæmoglobin of 9 g. per 100 ml., had been given a mixture containing ferrous sulphate and cobaltous chloride over a period of twelve weeks. The daily dose had been 0.5 ml. of the preparation—equivalent to 40 mg. of cobaltous chloride, or 4 mg. per kg. body weight. On admission to hospital she was found to have a severe degree of myxœdema, with considerable enlargement of the thyroid gland. Three days after admission she developed congestive heart failure. Treatment consisted in immediate discontinuation of the cobalt mixture and the administration of thyroid extract. The child made a complete recovery.

Colloidal Zinc Borate in Rhinology

SATISFACTORY results are reported by M. Aubert and G. Senechal (*Bruxelles-Médical*, January 1957, 37, 97) from the use of a 0.2% solution of colloidal zinc borate in the treatment of various forms of rhinitis. *In vitro* experiments are reported indicating that this solution does not interfere with ciliary activity. The solution was applied four or five times daily by atomizer or in the form of nasal drops. Of 10 cases of acute sinusitis, 10 cleared up when treated by five applications daily of this solution given by means of an atomizer. The remaining nine were treated by antral puncture and lavage. Good results were obtained in 25 out of 26 cases of mucopurulent rhinitis, and in 10 out of 18 cases of chronic purulent rhinitis after fifteen days' treatment. The solution was found of value in the postoperative management of patients who had undergone operations on the nose. It is also said to be of value in the symptomatic treatment of vasomotor rhinitis.

REVIEWS OF BOOKS

Diagnosis and Treatment of Peripheral Vascular Disorders. BY DAVID I. ABRAMSON, M.D., F.A.C.P. London: Cassell & Co. Ltd., 1957. Pp. xv and 537. Figures 80. Price £5 5s.

THE author of this volume states in his preface that his purpose has been to make knowledge of its contents accessible to the busy family physician. Britain's busy family physicians will note that the book has over five hundred pages and costs five guineas. It is really a comprehensive textbook suitable for detailed reading by trainees in consultant medicine and surgery and useful for reference by many others. The layout is unusual in that the anatomy and physiology are collected at the end instead of forming an introduction, presumably on the supposition that this facilitates the skipping which this section often gets in any case. Its comprehensive character is shown by the large amount of space devoted to pathological conditions of veins and lymphatics and by the inclusion of sections on erythema nodosum, glomus tumours and Bazin's disease, although the balance of emphasis is naturally weighted in favour of those aspects of the subject, and especially the investigation and medical treatment of arterial insufficiency, to which the author has himself made notable contributions.

There are good sections on the tests used for arterial insufficiency and a pleasing emphasis on the value of simple bedside observations such as the palpation of pulses and the assessment of temperature and colour as opposed to the more complex instrumental investigations so often overstressed. Treatment receives that detailed exposition (including even the names of the drug firms and instrument makers) which is so often lacking in British textbooks. The American authorship is also evident in the fact that the active treatment of chilblains is fobbed off with only four lines, and that acrocyanosis is listed among the 'rare vascular disorders affecting the extremities'. The late Sir Thomas Lewis would certainly have reacted violently to the prominence given to sympathetic hypertonus as a cause of disease. He might, however, have shed a tear to see intermittent venous occlusion so soon and so firmly linked with 'pavaex' boots and oscillating beds, and Buerger's exercises as agreeable occupations never yet proved to do harm.

This is, in fact, a good textbook on the subject by an author of experience and judgment, clearly written, well printed, and moderately well illustrated.

Human Ovulation and Fertility. BY EDMOND J. FARRIS, Ph.D. London: Pitman Medical Publishing Co. Ltd., 1956. Pp. xiii and 159. Figures 35. Price 50s.

THIS book can be regarded as a companion to the author's earlier volume on male fertility and, as did that volume, it collects together material most of which has already been published as papers in various medical and scientific journals. He is concerned mainly with a quest for precision in the diagnosis of the occurrence of ovulation and especially the close timing of that event. The key to this problem, in the author's hands, is the 'rat ovary hyperæmia test', which he devised and has now used with great effect since 1946. The reviewer has no doubt that the responses as described by Farris do indeed occur, but, for reasons which remain largely obscure, few other workers have been able to duplicate Farris's response. There is much else that is original in the book. Farris has devised a formula, based on his experiences with the rat test, for determining the optimum time of conception, and another which he considers to be an improvement on other methods of determining the 'safe period' for contraceptive purposes. He gives data on the effects of thyroid medication and of pituitary irradiation on the ovulation response as reflected by the rat test; and he describes a simple method of early pregnancy diagnosis which depends upon matching the colour of the cervix with a series of standards.

The book contains much of interest for all interested in problems of human reproduction.

Natural Childbirth. BY H. B. ATLEE, M.D., F.R.C.S. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications, 1956. Pp. v and 79. Figures 8. Price 21s.

THE term 'natural childbirth' covers a considerable body of ideas and practices and there is now a good deal of literature about it—too much, some may feel. Yet this is to be expected, since it concerns one of the inescapable, universal activities of life, one in which many emotions and ideas are involved. It is being thought about in many parts of the world, and different approaches are developing. This is all to the good, since the worst that could happen is that 'natural childbirth' should come to mean simply some particular cult or ritual. Yet since childbirth is so universal certain age-old observa-

tions hold true. It is interesting to see expressions of these emerging in the writings and conversations of practitioners of natural childbirth.

There is much in this book that is familiar, yet the author brings his own particular personality to bear on the subject. His methods are based on the pioneer work of Grantly Dick Read, to whom acknowledgment is properly given, but are influenced by Canadian practice which differs in some respects from ours. It lacks, for example, our excellent midwifery service and special arrangements have to be made to supply suitable companionship during the first stage of labour. The author makes some suggestions about ways of doing this. The mothers are given an analgesic agent only if they ask for it and are rather strongly warned of its dangers. This policy, as many of us know, can lead to a new source of tension, but here again it is due to the practice of the country where the author works, in which there has for some years been such an overdependence on analgesia that there is inevitably a reaction against it. There are some interesting suggestions about architecture and arrangement of a maternity unit.

The language is a little too conversational for some tastes but the observations are shrewd, practical and humane. All in all the book can be recommended as well as any other as a small but common-sense introduction to the subject.

Minimal Pulmonary Tuberculosis Found by Mass Radiography (Fluorography). By V. H. SPRINGETT, M.D., M.R.C.P. London: H. K. Lewis & Co. Ltd., 1956. Pp. xiv and 233. Illustrated. Price 42s.

This is a report to the Prophit Committee of the Royal College of Physicians of a follow-up of people found by mass radiography to have small tuberculous lesions. Cases were collected from one stationary and one mobile unit in London between January 1946 and October 1948 and were all followed up for at least five years. A period of rapid change in tuberculous therapy is thus covered, but during the initial years, during which the most important observations were made, chemotherapy was not used so that the survey does provide valuable information about the natural history of small tuberculous lesions in the absence of chemotherapy. The presentation is exemplary and provides full information and illustrations of the types of radiographic abnormalities included, the background, social and occupational, of the patients and the results of initial clinical and bacteriological findings.

The chest physician will find this book a rich source of information to which he will often wish to refer. The general practitioner will be

most interested in the final chapter on management where criteria are given for the important decision as to whether the discovery of a minimal tuberculous lesion should be followed by regular observation or active treatment. Dr. Springett is to be congratulated on an investigation that was skilfully planned and carefully executed and upon a clear and scholarly report.

Postural Drainage. By E. WINIFFRED THACKER, M.C.S.P. London: Lloyd-Luke (Medical Books) Ltd., 1956. Pp. viii and 56. Figures 37. Price 8s. 6d.

THE object of this publication is 'to illustrate the technique of postural drainage' as applied to the treatment of respiratory disease. After an introductory chapter on anatomy and physiology, the text is concerned with the principles governing postural drainage and the correct technique of breathing; throughout the emphasis is laid upon the practical aspect of the subject. The correct position to be adopted for the drainage of each individual lung segment is illustrated by a photograph beneath which is a diagram of the bronchus concerned. This expresses the matter in the clearest terms. Children, the elderly, and emphysematous patients are considered as special problems and many valuable hints are given on the management of such patients. Preoperative and postoperative treatment is given in detail with a separate reference to thoracoplasty and plombage.

This book is admirable and can be recommended.

Diseases of the Breast. By C. D. HAAGENSEN, M.D. Philadelphia and London: W. B. Saunders Co., 1956. Pp. xviii and 753. Figures 404. Price £5 12s.

THIS excellent book is above all a work of reference. The working surgeon will find practical information and wise advice in every chapter. The first, on the anatomy of the mammary gland, is masterly; it contains a welcome discussion, scholarly and factual, on the lymphatic drainage of the breast to the nodes along the internal mammary artery. The chapter on diagnosis is clear, and illustrated by excellent photographs. That on etiology contains convincing proof from many countries that normal function is the surest preventive of breast cancer. Chapter 19, on the natural history of cancer of the breast, is one of the most helpful—packed with the wisdom of experience. The account of the radical operation for cancer as performed by the author is the best written and the best illustrated description to be found in any book today.

Dr. Haagensen speaks with the great authority of the Presbyterian Hospital, and of a large

personal series, carefully recorded and analysed, behind him. He is an American and a Halstedian, with all that that implies. His results in cancer are better than most, but they involve a preliminary screening to exclude incurable cases which may involve biopsy of the intercostal nodes, and even drill biopsy of the lumbar vertebrae—precautions that few British surgeons would countenance. Like Halsted, his contacts outside the States are chiefly with the Continent of Europe. British surgery is seldom mentioned, and British figures are on the whole neglected.

Having made these unkind and insular comments, your reviewer would add that he has seldom enjoyed a book more or derived greater benefit. It is one that every library must buy and that every surgeon should read.

Lehrbuch der Tropenkrankheiten. Edited by PROF. DR. ERNST GEORG NAUCK. Stuttgart: Georg Thieme, 1956. Pp. viii and 432. Figures 125. Price DM 64.

This is the first textbook on tropical medicine published in the German language since 1942. It is a welcome addition to the literature on the subject. The skilfully and clearly written text is studded with useful diagrams and beautifully reproduced half-tone and coloured plates. The arrangement of the book is a little unusual in that there are no formal chapters, each subject being treated within certain major divisions as follows: arthropods as transmitters and vectors of disease; helminth diseases; protozoal diseases; spirochaetal diseases; bacterial diseases; rickettsial diseases; tropical virus diseases; mycoses; nutritional conditions; diseases of various etiologies (e.g. bartonellosis, tropical ulcer; poisonous animals). Professor Nauck is to be congratulated on a first-class book which covers the essentials of the subject with complete clarity.

Glasgow Common Lodging Houses and the People Living in Them. BY STUART I. A. LAIDLAW, M.D., PH.D., F.R.F.P.S.G., D.P.H., D.P.A. Glasgow: Health and Welfare Committee of the Corporation of Glasgow, 1956. Pp. 261. Illustrated. Price 30s.

STUART LAIDLAW's thesis, for which he was awarded the Ph.D. of the University of Glasgow in June 1955, only a few days before his untimely death, has been published on the instruction of the City's health and welfare committee. It is an account of a socio-medical survey designed to learn more about a little understood problem and its significance to public health. There has been nothing like it since Henry Mayhew's study of common lodging-houses in 'London Survey (1851-62)'. The City of Glasgow has 19 common lodging

houses with 4,893 beds and approximately 3,600 residents (of whom 400 are females). Laidlaw took a sample of 800, consisting of 20 per cent. of the men and 50 per cent. of the women. The sample was not random. It was carefully selected to ensure that it was 'a fair section of the inhabitants'. The interviewing covered three years and involved 700 visits. Many of the findings, upon which Laidlaw comments with shrewd perception, are of exceptional interest. The common lodging house, which takes the elderly and disabled, and much of the flotsam and jetsam of society, Laidlaw, as many before him, saw as an essential institution in an overcrowded city. Many of the inhabitants are of 'such low mental calibre and poor behaviour that they could reside nowhere else. To introduce them as lodgers into the family circle of a decent home would be to court disaster'. The alternative to the common lodging house, even in a welfare state, is not easy to find. Cheapness, privacy and liberty, the main assets, cannot easily be secured in other ways.

Laidlaw's survey will remain long as a monument to a medical officer of health, great even according to the standards and tradition of Glasgow.

Soranus' Gynecology. Translated by OWSEI TEMKIN, M.D. Baltimore: The Johns Hopkins Press; London: Cumberlege, 1956. Pp. xlix and 258. Figures 2. Price 40s.

WE have to thank the United States for several important ventures in rendering the Classics available to us in easily read editions. The Loeb series springs to mind as an example. Now we should be grateful to the team of experts who have produced this eminently readable edition of *Soranus' Gynecology*. The translation is the responsibility of Dr. Temkin, but he has been advised by Dr. Edelstein as a classicist, by Professor Eastman as an obstetrician, and by several other experts. The production reads as if it has been a work of pleasure and care. It should be read by every gynaecologist or practitioner who is interested in the history of his art, as Soranus was one of the most eminent medical writers of antiquity and was singularly free of superstition.

There is something almost touchingly Victorian here. On the one hand we have the interested band of workers in medical history undertaking the translation as an earnest group reminding us of times gone by in England, and on the other hand some of the advice of Soranus has a Victorian flavour too, for example his remarks on the choice of a wet nurse. The book reminds us that the great minds of the past could

arrange their thoughts on a scientific subject in a strikingly modern order and manner.

NEW EDITIONS

The Practice of Medicine, edited by Jonathan C. Meakins, C.B.E., M.D., LL.D., in its sixth edition (Henry Kimpton, £6) has an editorial board of 24, and a list of 86 contributors. The great majority of these are drawn from the United States, with a few from Canada and two from the United Kingdom. The names in the list of associate editors and contributors include some of the best known on the other side of the Atlantic. This, together with the skill with which Professor Meakins has managed his large team, has resulted in the production of a book which holds its place as one of the outstanding textbooks in medical literature. As a reference book, with the emphasis always on the clinical, rather than the theoretical, aspects of medicine, it can be unreservedly recommended to all physicians, whether in consulting or general practice.

Whitla's Dictionary of Medical Treatment in its ninth edition (Baillière, Tindall & Cox, 52s. 6d.) is edited by R. S. Allison, M.D., F.R.C.P., and T. H. Crozier, M.D., F.R.C.P., and has been entirely rewritten. To make room for advances in knowledge, surgical, gynaecological and ear, nose and throat topics have been omitted. It is difficult to realize that it is 66 years since this book first appeared. During the intervening years it has served many generations of practitioners as a useful authoritative, quick-reference guide to therapy. The new edition continues to subserve this useful function, and the Belfast Medical School has every reason to continue to be proud of this contribution to medical literature.

Progress in Clinical Medicine, edited by Raymond Daley, M.D., F.R.C.P., and Henry Miller, M.D., F.R.C.P., in its third edition (J. & A. Churchill Ltd., 40s.) maintains the high standard of its predecessors. The chapter on psychiatry has been omitted, to be replaced by two new chapters: one on 'the care of the aged', and one on 'radioactive isotopes in medicine'. The editors have been well served by their team of ten contributors. The general practitioner will find it a useful reference book.

An Introduction to Dermatology, by G. H. Percival, M.D., PH.D., F.R.C.P., D.P.H., in its twelfth edition (E. & S. Livingstone, 45s.).—This is the twelfth edition of the book published originally by the late Sir Norman Walker. In a book of this size it is always difficult to achieve a sense of balance but, as in previous editions, this balance has been well

maintained, the common things being dealt with fully whilst the rare exotic dermatoses are left for the large fully comprehensive tomes. The inclusion of erythema induratum scrofulosorum (Bazin's disease) in the sarcoid group of diseases is not in accord with generally accepted teaching. The illustrations are numerous. Those in colour are good with the exception of the histological pictures. The black and white photomicrographs are much better than the hazy coloured sections.

This book can be recommended to medical students and to those requiring, as the title suggests, an introduction to dermatology.

Textbook of Biophysical Chemistry, by Edward Staunton West, PH.D., in its second edition (Macmillan Co., 35s.) is a revised version of a book originally known as 'Physical Chemistry for Students of Biochemistry and Medicine'. It provides an excellent account of a number of physico-chemical topics together with discussions of their biochemical significance. Among the subjects with which the book deals are atomic structure and valence; gases and solutions; electrolytic dissociation; acids, bases and buffers; osmotic pressure; colloidal and membrane phenomena; chemistry of respiration, acid-base balance, electrolyte and water balance; biological oxidation and reduction; chemical energetics; the velocity of reactions. An important feature is that the author has wisely taken into account the possibility that the reader's knowledge of mathematics may be rather limited, and he has therefore stressed various points of elementary mathematics necessary for the understanding of the physical and chemical principles he is describing. This is an admirable book and one which can be recommended to all those who seek an introduction to biophysical chemistry which is both readable and authoritative.

Blakiston's New Gould Medical Dictionary, edited by Normand L. Hoerr, M.D., and Arthur Osol, PH.D., in its second edition (McGraw-Hill Book Co. Inc., 86s. 6d.) has been brought up to date and maintains its status as one of the standard reference books in medicine. It is said to contain 12,000 new terms. The laudable desire to be up to date has perhaps been carried to excess by the inclusion of drugs still in the experimental stage, but in a dictionary this is erring on the right side.

The contents of the April issue, which will contain a symposium on 'Radioactive Isotopes' will be found on page A120 at the end of the advertisement section.

Notes and Preparations see page 389.
Fifty Years Ago see page 393.
Motoring Notes see page A75.
Travel Notes see page A79.

Haemophilus influenzae

in chronic bronchitis this organism may be found in as many as 80 per cent. to 90 per cent. of patients with purulent sputum.

Lancet, 1954, ii, 739

Haemophilus influenzae

in acute mucopurulent tracheobronchitis *H. influenzae* may be isolated in about 83 per cent. of cases and in 48 per cent. in practically pure culture

Proc. Roy. Soc. Med., 1956, 49, 773

Haemophilus influenzae

may be inhibited *in vitro* by concentrations of *oleandomycin* as low as 0.078 microgramme/ml.

Antibiot. Ann. 1954/55 p. 287

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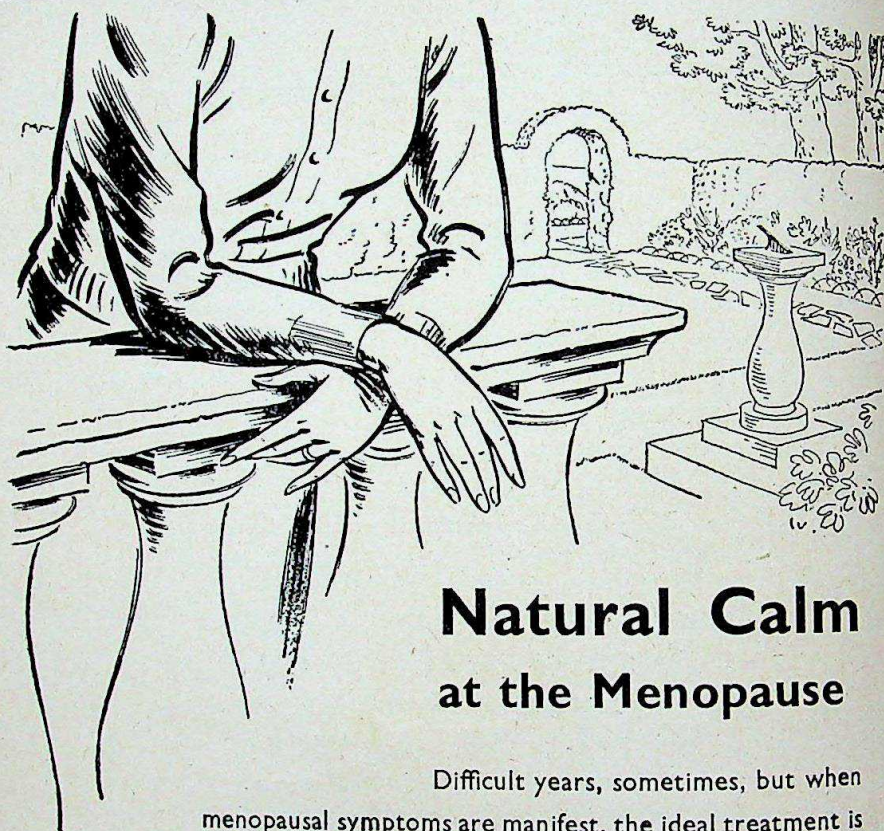
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NOTES AND PREPARATIONS

NEW PREPARATIONS

BIOTEXIN tablets each contain 125 mg. of the mono-sodium salt of novobiocin, which has extensive bactericidal activity against staphylococcal infections including those resistant to other antibiotics. Issued in bottles of 32 and 100 press-coated tablets. (Glaxo Laboratories Ltd., Greenford, Middlesex.)

COACTYL tablets each contain 0.5 mg. of prednisone, 300 mg. of acetylsalicylic acid, 160 mg. of aluminium hydroxide and 30 mg. of magnesium trisilicate. They are indicated in 'rheumatoid conditions of mild or average severity' and in 'allergies and hypersensitivity'. (Distributed by Fassett & Johnson Ltd., 86 Clerkenwell Road, London, E.C.1.)

EMERITAL tablets each contain 100 mg. of acetaminophen, 125 mg. of salicylamide, 125 mg. of phenacetin and 25 mg. of caffeine, and are intended for the treatment of primary dysmenorrhoea. Available in units of 6 tablets in sealed foil, in cartons of 30 and packs of 504. (M.C.P. Pure Drugs Ltd., 86 Strand, London, W.C.2.)

MATROMYCIN capsules each contain 250 mg. of oleandomycin, which is active against 'a wide range of gram-positive organisms, particularly staphylococci, streptococci and pneumococci' and also 'some gram-negative bacteria'. Issued in bottles of 12 and 100 capsules. (Pfizer Ltd., 137-139 Sandgate Road, Folkestone, Kent.)

PREMARIN 'intravenous injection' is a preparation of 'conjugated oestrogens (equine) specially prepared for intravenous injection', but it can also be given by the intramuscular route. It is said to have been 'used successfully in 'haemorrhages of the ear, nose and throat, gastro-intestinal system and genito-urinary system', and in 'intra-ocular haemorrhage, haematemesis and hæmoptysis due to carcinoma'. Issued in ampoules containing 20 mg. of water-soluble conjugated oestrogen expressed as sodium oestrone phosphate, with 5 ml. of sterile diluent containing 5% phenol. (Imperial Chemical (Pharmaceuticals) Ltd., Fulshaw Hall, Wilmslow, Cheshire.)

PHARMACEUTICAL NOTES

PURE DRUG CO. LTD. announce that secretin and pancreozymin are now available in a more stable form for clinical use in the investigation of disorders of the pancreas and gall-bladder. Secretin is supplied in 10-ml.

rubber-capped vials of 100 units, and pancreozymin in 25-ml. rubber-capped vials of 100 units, both preparations being in the form of powder. In this form they retain their activity almost indefinitely at room temperature or below. Detailed literature is available on request. (Station Street, Nottingham.)

CUXSON, GERRARD & Co. LTD. announce the introduction of the 'ampin' emergency tin for use in 'those first aid boxes and posts where morphine or its equivalent must be always at hand'. This contains, for subcutaneous injection, six 'ampins' of either morphine sulphate (16 mg.) or an equivalent dose of 'tetrapon' (a mixture of alkaloids of opium). Also included in the tin are six tie-on labels stating that morphine has been given, and on the inside of the lid there are clear pictorial instructions for use. (Fountain Lane, Oldbury, Birmingham.)

HANWORTH FOOD PRODUCTS LTD. announce the introduction of their 'dietade' range of 'canned foods for sodium reduced diets'. No salt is added to the products but 'a full flavour is nevertheless achieved by the use of sodium free condiments'. The average sodium content is 1 mg. per ounce. The first of these foods to be issued are 'processed peas, garden mint flavoured' and 'beans in tomato sauce'. Available in tins of 8 oz. and for hospital use in tins of 16 and 30 oz. (Dietetic Foods Division, Colnbrook, Bucks.)

PFIZER LTD. announce that their hydrocortisone preparation, 'cortril', is now available in the form of a lotion. This is in two strengths (0.5% and 1% of hydrocortisone free alcohol in an aqueous vehicle) and is supplied in 20-ml. plastic bottles. (137-139 Sandgate Road, Folkestone, Kent.)

WARD, CASSENNE LTD. announce the introduction of 'deltalone' brand prednisone and 'hydrodeltalone' brand prednisolone. Both preparations are available in buffered tablets of 1 mg. or 5 mg., in bottles of 30, and 'hydrodeltalone' is also available as an ointment (tubes of 5 g. or 15 g.), as an eye ointment (tubes of 3 g.), as eye drops (bottles of 3 ml.) and for intra-synovial injection (vials of 3 ml.). (Distributed by Fassett & Johnson Ltd., 86 Clerkenwell Road, London, E.C.1.)

FORTHCOMING CONFERENCES

THE International Society for the Welfare of Cripples will hold its seventh world congress at

Church House, Westminster, London, S.W.1, from July 22 to 26, 1957. The general theme will be 'Planning for Victory Over Disablement'. Registrations must be received by May 1. Further details may be obtained from the Congress Secretary, 34 Eccleston Square, London, S.W.1.

An International Symposium on Psychotropic Pharmacology will be held in Milan from May 9 to 11, 1957. Registrations must be received by April 15. Full details may be obtained from the Secretariat, Via A. del Sarto, 21, Milan.

The Promotion of Health will be the subject for discussion at a summer school organized by the Central Council for Health Education, to be held at Reichel Hall, University of North Wales, Bangor, from August 20 to 30, 1957. Application forms and further details may be obtained from the Medical Director, Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1.

PRESCRIPTIONS FOR DIABETICS

THE medical subcommittee of the British Diabetic Association has now clarified with the Ministry of Health some financial alleviations for diabetic patients on the new prescription regulations. The position now is that supplies of needles, spirit, testing tablets and insulin can be prescribed for three months or more, depending upon the doctor's view in the individual case. One shilling only per item will be payable irrespective of the quantity ordered.

HOSPITAL COSTS IN SCOTLAND

THE average weekly cost of maintaining a patient in general hospitals in Scotland (excluding the major teaching hospitals) during the year ended March 31, 1956, was £16 os. 6d., an increase of 6.9% over 1954-55. The comparable cost in the teaching hospitals was £17 6s. 10d., an increase of 5%. The cost varied considerably in different types of hospitals, ranging from £5 1s. 0d. in mental deficiency hospitals to £19 19s. 4d. in maternity hospitals. For every £1 spent in treating and maintaining an inpatient (excluding specialist service salaries), 10s. 10d. was spent on salaries and wages, 3s. 1d. on provisions, 1s. 5d. on drugs, dressings, patients' clothing, and bedding, 2s. 6d. on domestic repairs, and 2s. 2d. on overheads. The cost for each out-patient attendance was 8s. 8d.

THE DOCTOR'S DISEASE

IN Scotland the death rate from all causes is highest among the professional and managerial classes, according to the annual report for 1955 of the Registrar General for Scotland. Within

this group, however, there are wide differences. The death rate is well below the average among teachers and scientists, but well above the average among managers, doctors, and middle-grade and senior civil servants because of the particularly high incidence of coronary thrombosis among them. Coronary thrombosis remains the principal single cause of death among all classes, higher rates from this cause occurring mostly among persons in occupations which do not involve physical labour. Doctors head the list, with a rate more than 70% above normal. They are closely followed by senior civil servants and managers. Figures for deaths from carcinoma of the lung show that these are less frequent amongst agricultural workers than any other major group.

There is a noticeable tendency towards earlier marriage. In 1954, the latest year for which figures are available, 45% of the men who married were under 25, compared with only 28% in 1938. The comparable figures for women are 65% in 1954 and 49% in 1938. Despite this tendency towards earlier marriage, the proportion of married persons in the population between 15 and 20 is still a good deal lower in Scotland than in the other main English-speaking countries.

CANCER OF THE BREAST AND UTERUS

BETWEEN 1920 and 1953, cancer of the breast mortality increased by more than 100% in most countries, including Denmark, Australia and New Zealand, and increased by more than 50% in the United Kingdom, Switzerland and the United States. These figures are given in a review of the subject by Dr. M. Pascua, director consultant on health statistics for the World Health Organization (*Bull. Wld Hlth Org.* 1956, 15, 5). The lowest death rate was in Japan (3.3 per 100,000 women), whilst the highest rates were in England and Wales (35.7), Denmark (32), Scotland (30.8) and Switzerland (30.5).

In the case of cancer of the uterus, mortality has either been stationary or has actually decreased. The most definite decline has been in England and Wales, Scotland, Switzerland and the United States. An exception to this tendency is Denmark where the crude mortality rate has increased somewhat. In 1953, the mortality rate for cancer of the uterus was 22.6 per 100,000 women in Denmark, compared with 19.3 in the United States, 17.8 in Scotland, and 10.9 in Ireland.

DONOR EYES FOR CORNEAL GRAFTS
THERE is still a shortage of donor eyes for corneal grafts, according to G. J. Roman



THE timely administration of 'S-Mez' in the treatment of the pneumonias, bronchitis, tonsillitis and upper respiratory infections, undoubtedly gives the best chance of a rapid recovery.

Furthermore, a small daily prophylactic dose of 'S-Mez' is of considerable benefit in children subject to recurrent infections of the upper respiratory tract, especially when they are awaiting tonsillectomy and to prevent the recurrence of rheumatic fever.

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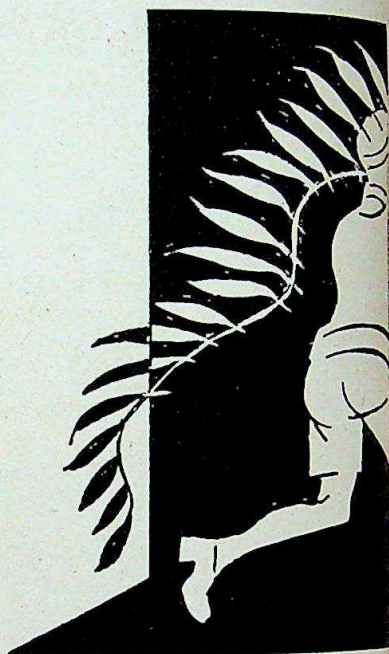


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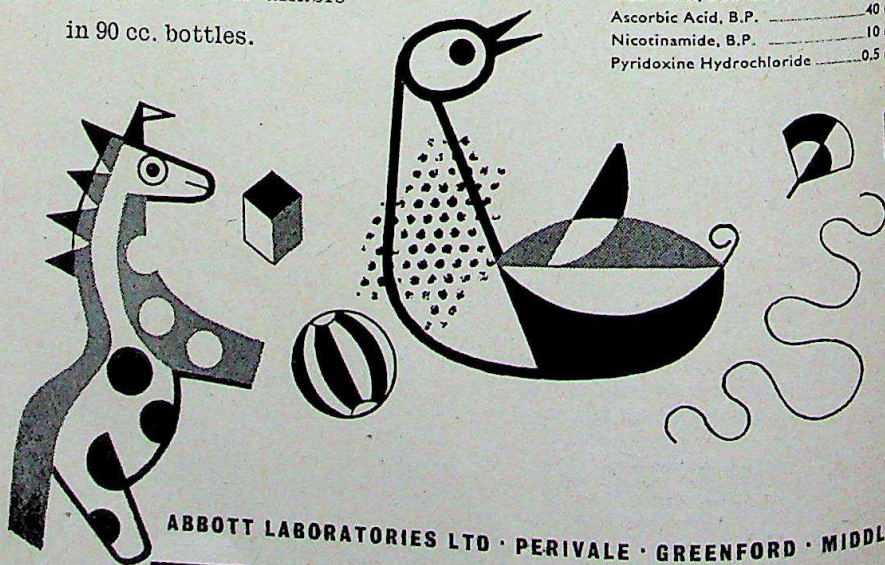
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This pleasant vitamin supplement can
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Aneurine Hydrochloride B.P.	1.5 mg.
Riboflavine, B.P.	1.2 mg.
Ascorbic Acid, B.P.	40 mg.
Nicotinamide, B.P.	10 mg.
Pyridoxine Hydrochloride	0.5 mg.



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N.O.T.B.A. Bulletin, January 1957). The number of eyes donated rose to 118 in 1953, the year in which the Corneal Grafting Act came into force, but fell to 50 in 1954. The latest available figures show that 83 eyes were donated in the first half of 1956. It is suggested that practitioners can help considerably by mentioning the matter of becoming a donor to their patients. The sooner the eye is removed the better, and the upper limit is usually within ten hours of death. The donor eye should be healthy and without corneal scars or other lesions. The presence of a fundus or other intra-ocular abnormality, apart from inflammation, is of little consequence. Donor material from old persons is more suitable than when obtained from the very young.

ANTIBIOTICS IN FRANCE

The use of the tetracyclines is falling off in Paris, according to Raymond Charonnat, the Director of the Central Pharmacy of the Hôpitals of Paris (*Bull. Soc. med. Hôp. Paris*, 1956, 72, 877). His figures are based upon the amount of antibiotic supplied by his pharmacy to the public assistance hospitals in Paris. These figures show that the amount of penicillin supplied annually rose from 0.3 kg. in 1946 to 1.225 kg. in 1954, and fell to 734 kg. (1,225 milliard units) in 1955. Consumption of streptomycin (including dihydrostreptomycin) has risen steadily from 0.7 kg. in 1946 to 1,148 kg. in 1955. After a slow start, increasing only from 0.1 kg. in 1949 to 71 kg. in 1951, the consumption of chloramphenicol has risen rapidly and steadily, being 284 kg. in 1955. The consumption of the three tetracyclines (chlortetracycline, tetracycline, and tetracycline), on the other hand, has been falling off during recent years. It reached a peak of 547 kg. in 1952, but by 1955 had fallen to 242 kg. per annum.

PHARMACEUTICAL EXPORTS

British exports of drugs and medicines reached a new record in 1956 of £35,943,000. Of this total, antibiotics accounted for nearly £7 million, and sulphonamides for nearly £3 million, and sulphonal for £1½ million. Australia and India were the leading export markets. Sales to Egypt were halved, but sales to the United States were nearly £1 million, thus surpassing last year's record of £660,000.

'THE ROUND TABLE'

Dr. Robert M. Green, as renowned for its culture as for its medical acumen, is the appropriate home for a 'Round Table'. An Arthurian Romance Epic', by Robert M. Green (Privately printed by the Green Press, Jamaica Plain, Boston, Massachu-

setts). Dr. Green was a brilliant alumnus of Harvard, and is best remembered there as an outstanding instructor in anatomy. While still an undergraduate he became interested in the Arthurian romances. This volume—the first of five—is the result. The writing of this epic poem—there are 20,000 lines in the present volume—occupied his leisure moments throughout his life. He did not live to see the first volume published, but it is hoped to publish the remaining four in the course of time. The first volume represents a remarkable achievement and is a notable tribute to the scholarship and literary gifts of the author.

A CAUTIONARY TALE OF DDT

In an interview with a correspondent of the *Financial Times*, Dr. Carl Koechlin, the chairman of the Geigy Company, recalls how, when the unique qualities of DDT as an insecticide were discovered in the early days of the 1939-45 War, he went to Bern to talk to the British Legation and to offer his company's new product for the British war effort. The reply he received from the British Military Attaché was: 'We have no time for this sort of thing now. You had better come back after the end of the war!' Fortunately the reception of the same offer by the American Legation and by our Ministry of Production was very different, and within a few months thousands of tons of DDT were being produced for the use of the Allied Forces.

PUBLICATIONS

Anæmia and the Alimentary Tract, by L. J. Witts, D.M., is an expanded version of the Sydney Watson Smith Lecture delivered before the Royal College of Physicians of Edinburgh in 1955. In its expanded form it provides an authoritative review of a subject which the author has made particularly his own. (Royal College of Physicians of Edinburgh, price 7s. 6d.)

The Person behind the Disease, by Julius Bauer, M.D., F.A.C.P., is about the genetic uniqueness of the individual except in the case of uniovular twins, to which there are only five references. It focuses with erudition a subject which in a more or less blurred form is rarely absent for long from the general practitioner's mind during his working and cogitating hours. It can become obessional, so that we see our patients cast in a genetic mould, condemned to play a predestined part, mere mechanisms, but this book with its two coatings of culture, from the old world and the new, modifies that view. The author takes the ancient and modern holistic view of medicine. (Grune and Stratton, Inc. Price \$3.50.)

Emmetropia and Its Aberrations (M.R.C. Special Report Series No. 293), by Arnold Sorsby, B. Benjamin, J. B. Davey, M. Sheridan and J. M. Tanner, is based upon the proposition that the shortest way to an understanding of the whole range of abnormal eyesight (the ametropias) may lie in the study of so-called normal eyesight (emmetropia). It is an authoritative study carried out with meticulous care and judicious assessment. (H.M. Stationery Office, price 7s. 6d.)

Disease Control and International Travel, by H. S. Gear and Z. Deutschman, is a reprint of a special number of the *Chronicle of the World Health Organization* (1956, 10, 273-340). It is an admirably written review of international sanitary regulations, and will be read with interest by many doctors other than medical officers of health and colonial medical officers. (H.M. Stationery Office, price 3s. 6d.)

'*The Compound*', compiled by W. Hetherington, F.P.S.—An Addendum for 1956 has been published to this 'compendium of ethical proprietaries used in medicine and pharmacy'. (John Wright & Sons Ltd., price 4s.)

Family Medical Costs and Voluntary Health Insurance: A Nationwide Survey, by Odin W. Anderson, PH.D., and Jacob J. Feldman, is described as 'the first nationwide survey of family costs since 1933' in the United States. The survey was sponsored by the Health Information Foundation, of which Dr. Anderson is the research director. It is based upon a survey of 8,898 individuals in 2,809 families. As the survey was made in 1953, many of the actual figures are probably out of date by now, but the general over-all picture is probably still valid. As a picture of one facet of American medicine it will be read with interest by many in this country. It shows, for instance, that in the year ended July 1953 the American people incurred charges for all personal health services in the neighbourhood of \$10.2 billion, which represents 4% to 5% of the total national income. This percentage has remained remarkably stable during the last twenty-five years. (McGraw-Hill, price 49s.)

Children Who Wet Their Beds, by Dr. Portia Holman, is intended for the mothers of these unfortunate children. It is one of the 'parent guidance series' published by the National Association for Mental Health, and contains sound practical advice couched in simple language. (Family Health Publications, Maurice Craig House, 19 Queen Anne Street, London, W.1. Price 1s. 3d.)

Occupational First Aid has been prepared as a manual to be used in conjunction with the first-aid courses for workers in industry now being organized by the St. John Ambulance Association, the St. Andrew's Ambulance Association and the British Red Cross Society. In a foreword, Dr. E. R. A. Merewether, H.M. Senior Medical Inspector of Factories, commends it to all employers and their first-aid personnel. (St. John Ambulance Association, St. John's Gate, Clerkenwell, London, E.C.1. Price 2s.)

Harlow 1957.—This brightly coloured, profusely illustrated and glossy-papered guide is the most publicized of the 'new towns' make fascinating reading. As a social experiment Harlow is very definitely 'on the map'. Mistakes have been made, but the members of the development corporation have been the first to admit this and—to their credit—to learn from them. No-one can afford to miss reading this guide to a brave new world. (*The Harlow Citizen*, 23 East Gate, The High, Harlow. Price 3s. 6d.)

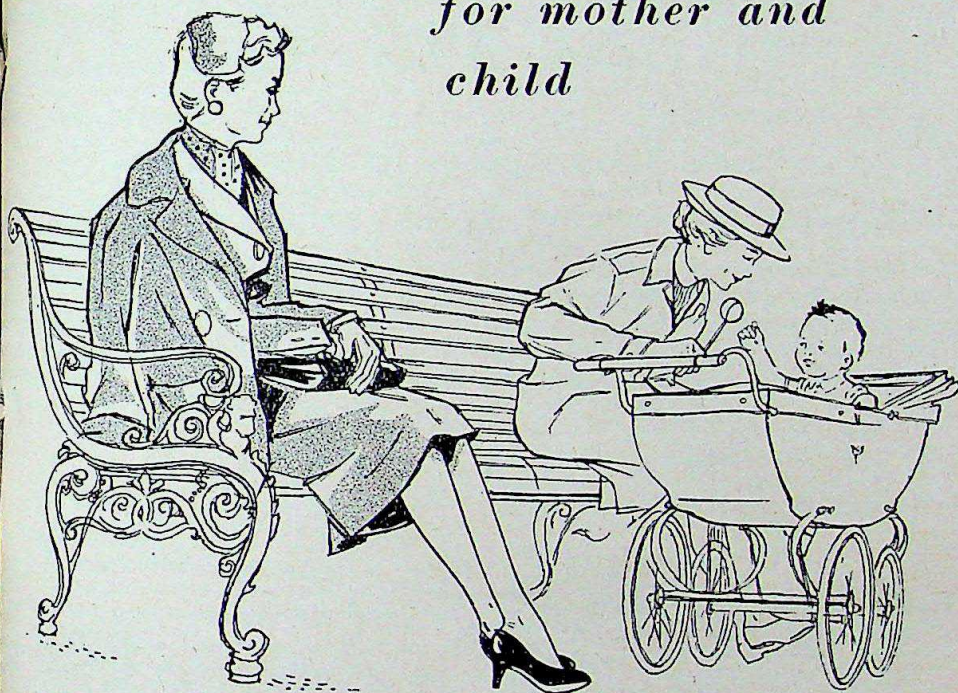
OFFICIAL NOTICE

Trainee General Practitioners (E.C.L. 7/57)

In view of the recommendations in the report of the trainee general practitioner subcommittee of the British Medical Association, the Ministry of Health has agreed with the representatives of the profession to the following modifications in the conditions which he has previously had down. (a) The doctor should normally have less than 2000 patients on his list if he practices in an urban area, or 1,500 if his practice is rural. In particular circumstances, slightly smaller lists may be accepted, provided that the executive committee, after consultation with the local medical committee, are satisfied that the practice is of a kind which will provide adequate opportunities for training in all aspects of a general practitioner's work, including the organization of a general practice. (b) The general practitioner will be payable on condition that a doctor who is approved as a trainer, and who appoints a trainee, does not, during the time the latter is with him, reduce the amount of his appointment which he already had at the time of his appointment.

CORRIGENDUM.—Mr. D. Ranger writes: 'In my entry on "Vincent's angina and agranulocytic angina" in *The Practitioner*, 1956, 177, 685 I included erythromycin in the list of drugs responsible for agranulocytic angina. Although some depression in the white count has been recorded in very rare instances, I am now informed that there is no case on record of erythromycin having caused agranulocytosis.'

Timely insurance for mother and child



The modern management of pregnancy has been shown to pay rich dividends in health and well-being to both mother and child. As the demand for the chief dietary factors may be increased during pregnancy up to 100 per cent, the timely administration of additional vitamins, bone-forming minerals and haematinic factors is a wise nutritional insurance. PRENATAL CAPSULES Lederle contain all these essential factors, and the simple routine of 2 Capsules daily from the time pregnancy is confirmed and through the period of lactation, provides adequate nutritional insurance for the mother, leads to healthy lactation and to progressive weight gains in the child. The Capsules are dry-filled to ensure rapid assimilation of ingredients and to avoid any unpleasant regurgitation.

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Vitamin A	2,000 I.U.
Vitamin D	400 I.U.
Thiamine HCl (B ₁)	2 mg.
Riboflavin (B ₂)	2 mg.
Ascorbic acid (C)	35 mg.
Niacinamide	7 mg.

Vitamin B ₁₂	1 microgram
as present in concentrated extractives	
from streptomyces fermentation	
Vitamin K (Menadione)	0.5 mg.
Folic acid	1 mg.
Calcium (in CaHPO ₄)	250 mg.
Phosphorous (in CaHPO ₄)	190 mg.

Dicalcium phosphate anhydrous	
(CaHPO ₄)	869 mg.
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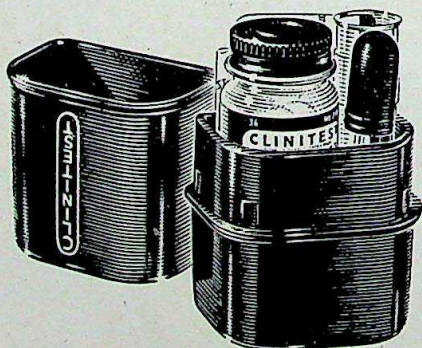
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THE PRACTITIONER

Fifty Years Ago

'The more ancient the abuse the more sacred it is'.—Voltaire: *Les Guèbres*.

MARCH 1907

Editor discusses 'Economic aspects of medical practice' in a realistic manner which will strike a sympathetic cord in many readers today: The eternal question of hospital abuse is at present going through one of the periodical crises of acute exacerbation which diversify the course of a chronic grievance of the medical profession . . . The passage of resolutions declaring that excessive medical charity is an evil, and that hospitals are misused, may relieve the feelings of a meeting, but has no appreciable influence on public opinion . . . To the people at large the matter is only a doctors' grievance and, for this view, wrong as it is, the profession is mainly itself to thank. Beneath the surface of altruism there runs a current of assumption that the public is under a special obligation to the profession which gives every practitioner a right to a living wage. It would be well if it were clearly recognized that doctors have no better claim to the patronage of the public than bakers or butchers . . . Medical practice is subject to the same rigid economic laws as every other calling in which man earns his bread by the sweat of his brow. It is a struggle in which the race is to the swift and the battle to the strong, and in which the weak are thrust aside and fall by the way . . . Medicine has the immense advantage of many other avocations in that it is not a luxury but a necessity. This does not mean, however, that every man who chooses to make a profession is necessary. He has to justify his existence by his work . . . It is, of course, undeniable that hospitals are to some extent misused . . . Sometimes, if the truth must be told, the out-patient room is the receptacle of "squeezed oranges" of general practice . . . not only in the out-patient department that the patient has an opportunity of learning "the daily task, the trivial round" of the duties that fall to him as a general practitioner . . . the remedies for the hospital grievance that have recently been proposed are all more or less impracticable. Compulsory insurance would deprive the practitioner's fees, but it could not deprive the person insured to seek counsel of him. How is insurance to be compelled? The free independent Briton will not, like the sublimely Teuton, go in State-leading strings . . . public medical service would mean contract practice writ large, with all its inherent evils immensely aggravated . . . Municipal control

would degrade the profession and hinder the progress of science. State control might be less objectionable, but the examples of hospitals in foreign countries tend to show that patients are not so well off under a government administration as they were under our own voluntary system'.

'The deputation from the Betterment of London Association which asked the Home Secretary to do something to abate the concourse of anything but sweet sounds, which make our streets places of torment to any but the deaf,



Sir Arthur Hall, M.D., F.R.C.P. (1866-1951).

got little encouragement from Mr. Gladstone. The motor bus has come to stay, and it can only be hoped that, as the machinery is perfected, it will cease to cleave the general ear with horrid din'.

One of the more interesting 'Original Communications' this month is a clinical lecture, 'Some Points Connected with Embolism', by Arthur Hall, M.D., F.R.C.P., Physician, Sheffield Royal Hospital, who reports three cases of fatal pulmonary embolism: 'In each of them

death was quite unexpected, there was nothing to call attention to a thrombus being in the process of formation. In each of them, the embolism occurred just after the night's rest, on slight movement, not getting up, merely sitting up in bed'. Arthur John Hall, the son of a Sheffield surgeon, was born in 1866 and was educated at Rugby, Cambridge, and St. Bartholomew's Hospital. Returning to Sheffield, he played a leading part in founding Sheffield University, held various chairs in the Medical School, and was physician to the Royal Hospital. When encephalitis lethargica appeared in Britain in 1918, he was one of the first to describe its symptoms. A cultured and kindly personality with a delightful sense of humour, 'Long Arthur' died in 1951, aged 84.

Charles Leedham-Green, F.R.C.S., Surgeon to the Queen's and Children's Hospitals, Birmingham, and Assistant Lecturer in Bacteriology, Birmingham University, discusses 'The Antiseptic Action of Metallic Sutures'. He was a pioneer in the use of the cystoscope and advocate of methylated spirit for sterilizing the hands before operation, but as a teacher his students found it difficult to follow his line of thought. In his review article 'Diseases of the Stomach', F. Craven Moore, M.D., M.R.C.P., Lecturer in Medicine, Manchester University, refers to Hermann Sahli's recently introduced

method for determining the functional capacity of the stomach by means of 'desmoid capsules' containing iodoform or methylene blue.

Sir William Read ('Some Famous Quacks' was 'one of the most successful quacks of whom there is record. The fact that he was grossly ignorant—being, it is said, unable even to read—only makes his success in gaining fame, wealth, and a title, all the more extraordinary'.

Only two books are reviewed this month, the first at great length. 'Nervous Diseases in Childhood and Early Life' by James Taylor, Physician for Out-patients to the National Hospital, Queen Square, 'is an extremely well-written and mostly up-to-date account . . . We think it scarcely advisable to devote eighteen pages to the discussion of Syringomyelia, a disease which practically never shows symptoms before the age of fifteen, and usually much later . . . We recognise here a tendency of the author to unduly enlarge upon a pet theme, and to quote overfully from previous work of his own upon this subject . . . The style of the book is most readable'. F. Frühwald's 'Reference Handbook of the Diseases of Children' is described as a 'ponderous tome . . . well printed and well illustrated. But having said thus much, we find it difficult to say much more in its favour'.

W. R. B.

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THE MONTH

It was only in 1948 that artificially produced radioactive isotopes became available for use in medicine in Great Britain. Today they are in use in every teaching hospital—and many others—in the country.

The Symposium This is the justification for devoting an entire symposium to the subject. Not that many doctors will ever handle radioactive isotopes personally, but it is essential that they should know something about them, and particularly about their use in therapy. For an intelligent understanding of their use a working knowledge is necessary of the principles involved, and to many doctors, particularly those of the older generations, the physics of radioactivity are wrapped in mystery. It is for this reason that we have introduced the symposium with three articles dealing, respectively, with the nature, the preparation, and the action of radioactive isotopes. These three articles, each written by a recognized authority on the subject, provide a simple straightforward account of the principles of radioactivity which should go far towards clarifying a highly complex subject. The following article on 'radioactive isotopes in research' indicates the tremendous potentialities of radioactive isotopes in the clarification of many outstanding biological problems.

The remainder of the symposium is devoted to the actual use of radioactive isotopes in clinical medicine. Perhaps most significant of these is that on 'a hospital radioactive unit'. The mere fact that such units now exist indicates the great advance that has been made in this field during the last decade. Equally significant is the inclusion of an article on 'radiography with radioactive isotopes' in the symposium. As the spectre of atomic warfare encircles the globe, it is with pride that Medicine and its associated sciences can note the progress that has been made in the harnessing of this new power to the service of humanity and the alleviation of suffering. We in this country can be particularly proud of the fact that, as pointed out by Dr. Seligman, 'Great Britain is by far the greatest isotope exporter in the world today'.

In 1953-54, the University of North Carolina carried out an investigation of general practice in North Carolina. The results of this investigation, based upon the findings in 94 practices, have now been published in the December 1956 issue of the *Journal of Medical Education*. The report presents a picture of present-day practice in the United States which will be of interest to all practitioners in this country. At the same time it has many lessons for those concerned with the future of general practice in this country. The differences

between practice in our two countries are striking, but largely superficial. Perhaps the most striking difference is in the equipment considered necessary in the United States. Thus, 42.6 per cent. of the North Carolina practitioners owned an electrocardiograph, 42.6 per cent. an x-ray machine, and 35.1 per cent. a B.M.R. apparatus. The reading habits are also somewhat different: the average number of journals purchased per practitioner was 4.09; 17.2 per cent. of practitioners purchased five to six journals, whilst as many as 7.5 per cent. purchased seven to fifteen journals. The only two British journals included in the list are *The Lancet* and *The Practitioner*. In view of the once much-publicized criticism of standards of 'surgeries' in this country, it is of interest to note that in North Carolina 'considerable variation was noted in the appearance of these practitioners' offices. The majority were clean and attractive. Some, however, were only clean and neat and gave little evidence of thought for patient comfort. Almost a third of the offices visited might be properly considered as unacceptable for the use to which they were put'.

Perhaps the most important point of all in this report is the doubt thrown upon the value of postgraduate study unless carefully controlled. The collected evidence is taken to 'suggest that doctors who do more than sixty hours of postgraduate study annually may be doing more than is necessary for their purposes, or that interest in medicine or study may not be their primary motivation in attending medical meetings . . . It cannot be denied that postgraduate education may have a favourable effect on the doctor's practice but such an assumption could be held with greater certitude if increasing amounts of formal postgraduate education were accompanied by better performance'. Equally thought-provoking in these days of universal planning is the finding that 'there were physicians who had been good medical students and had received good training, who were not exceptional physicians. There were others whose performance as students was unusually poor, whose internships were of indifferent quality, who nevertheless became superior physicians'.

THE tale of 'Johnny Notions' is a salutary reminder that the shrewd acumen of our forefathers could produce results which compare most favourably with those obtained in these days of 'scientific medicine'. **A Versatile Vaccinator** 'Johnny Notions', whose real name was John Williamson, was so-called by his neighbours because of his 'various attainments and superior talents'. According to his parish minister, he was 'a singular instance of an uncommon variety of talents, being a tailor, a joiner, a clock and watch mender, a blacksmith and a physician'. These laudatory comments are taken from the account of the united parishes of Mid and South Yell in the Shetland Islands contributed by the parish minister to the Old Statistical Account, 1792.

According to this account, which is quoted in the *Health Bulletin* (1957-

15, 2) issued by the chief medical officer of the Department of Health for Scotland, the population of these two parishes had increased considerably of late years, and one of the reasons given for this increase is 'the amazing success, with which inoculation has been attended. Formerly, the smallpox occasioned the most dreadful ravages in these islands; frequently carrying off a fifth part of the inhabitants. Now, hardly any suffer by this disorder'. The greater part of the credit for this is attributed to John Williamson. 'Unassisted by education, and unfettered by the rules of art, he stands unrivalled in this business. Several thousands have been inoculated by him and he has not lost a single patient'. Details are given of his technique. He insisted on 'the best matter', and kept it for seven to eight years before using it. To lessen its virulence he dried it in peat smoke and then buried it under ground, covered with camphor. Having made the inoculation, 'the only plaster he uses, for healing the wound, is a bit of cabbage leaf'. In the best tradition of Scottish medicine he was a therapeutic nihilist, and administered no medicines. It is claimed for him that 'it is particularly remarkable, that there is not a single instance in his practice, where the infection has not taken place, and made its appearance at the usual time'.

'ROUTINE "broadcasting" of the surgical patient's heart' is recommended by G. D. Fish, Jr., and his colleagues (*Ann. Surg.*, 1956, **144**, 1013) as a simple, yet effective, means of giving immediate warn-

Amplified Auscultation and the Surgeon

ing of cardiac arrest, or of impending arrest, to the anæsthetist. They give full details of the machine they have produced for this purpose and which they have now used in over a hundred cases. An ordinary diaphragm-type stethoscope head is attached to a pencil microphone by neoprene tubing. As the signal generated by the microphone is of the order of one-thousandth of a volt, it is perfectly safe under all conditions of operating-room use. Not only is the instrument easy to apply but in addition it is claimed that it 'is in no way an encumbrance either to the anæsthetist or the operating team'.

Many will probably question whether yet another 'gadget' in the overcrowded operating theatre is really necessary. On the other hand, in view of the increasing complexity of surgical operations, many of which can now be safely carried out on individuals who not so very long ago would have been considered 'bad risks', any reasonable means of helping to ensure that cardiac arrest is detected at the earliest possible moment is deserving of careful consideration. An incidental use of this new instrument is in the instruction of students and trainee surgeons in the importance of gentle handling of the anæsthetized patient. Rough handling of abdominal wounds, for instance, is 'reflected in the amplification of extraneous sounds superimposed on the normal heart sounds', whilst 'any pressure on the chest, as from an assistant's elbows while holding a retractor, is heard over the

loudspeaker'. May the time yet come when candidates for surgical appointments will be required to perform an operation while the selection committee listens in to the 'noises off' produced over the cardiac loudspeaker?

THE modern pharmacy, with its chromium-plated dispensary approached through rows of elegantly packed proprietary preparations, is a very different place from the chemist's shop of the turn of the century, with its 'jug and bottle' trade. In a recent issue of the *Chemist and Druggist* (1957, 167, 164) an octogenarian pharmacist recalls his memories of the period between 1890 and 1914. Household remedies then bulked large in the day-to-day business of the druggist: e.g. 'Four pennyworth each of oil of aniseed, oil of peppermint, laudanum, and paregoric, to be mixed with sugar syrup for a cough mixture'. Another common request was for '4 ounces of linseed oil'; this was for an infusion in which were dissolved 1 ounce of solazzi liquorice and 4 ounces of sugar candy for a cough mixture. The demand for ointments was not large, and those that were most popular have passed into the limbo of the past: 'trooper ointment' (for crab lice), 'white sipity' (for head lice), and basilicon (for drawing a boil). A favourite remedy for chilblains and chapped hands was camphor 'ice' or 'ball'. Penny boxes of pills were always in demand, and camphorated oil was so popular that it was made up in lots of 4 gallons at a time. 'Effervescent mag. cit.' was a ready seller in the summer—as a drink, not as a medicine. So long as it fizzed, and was tart and sweet, no questions were asked as to its constituents.

Cosmetics as known today were quite unknown, but there was a steady demand for perfume. A common request by the ladies on a Saturday night was 'sixpennyworth of perfume in a measure', from which it was promptly sprinkled by the lady on to her dress. Practically the only cosmetics sold were 'threepennyworth of carmine', *poudre de riz*, and peach bloom. Another popular request on Saturday nights was hair oil (olive oil and citronella), for which the customer brought his own bottle, and glycerin and rose water sold freely. Medicines and perfumes were by no means the only articles on sale in those days. For the dyeing of black dresses there was a regular demand for logwood chips (to make infusion for the dye) and green crystals (ferrous sulphate) for the mordant. Brunswick black was in demand every spring to 'revive the ubiquitous iron fireplace'. When red cabbage and onions were in season, a frequent order was 'a quart of vinegar and 4 ounces of mixed spices'. Occasionally there would be a request for 'essence of smoke' (pyroligenous acid) for giving a smoky flavour to a home-cured ham. Few pharmacists will regret the passing of the 'jug and bottle' trade, but the regimented citizen of the modern welfare state must be allowed to shed a tear for the passing of these old Dickensian days.

WHAT IS A RADIOACTIVE ISOTOPE?

By J. ROTBLAT, D.Sc.

*Professor of Physics, The Medical College of St. Bartholomew's Hospital,
University of London*

THE term isotope means 'the same place', and is used to denote those substances which occupy the same place in the periodic table of elements. The various elements which occur in nature are distinguished according to their chemical properties, and these can be simply explained by the structure of their atoms.

THE ATOM

Every atom consists of a central nucleus, and of a number of electrons revolving round it. This number of electrons is the main factor which determines the chemical properties of an element, because chemical reactions are due to an interchange of electrons between the atoms of the interacting elements. All the atoms of one chemical element have the same number of electrons, and this number, which is called the atomic number, defines the numerical place which the element occupies in the periodic table.

The atoms of a chemical element need not have the same structure; they may, for example, differ in weight. Since the weight of an atom has a negligible effect on chemical interactions, such atoms will behave chemically and biologically alike. The mass of the atom is concentrated in the nucleus and a difference in weight means a difference in the structure of the nucleus. The nuclei of atoms are made up of two types of particles, protons and neutrons (fig. 1), which have approximately the same weight but differ in their electrical properties, the proton has a positive charge—equal but opposite to that of the electron—whilst the neutron has no electrical charge. In every atom the number of protons in the nucleus is equal to the number of electrons revolving round it, i.e. to the atomic number. The total number of protons and neutrons is approximately equal to the atomic weight of the element, and is known as the mass number. Sodium, for example, which is element no. 11, has a mass number 23; this means that its nucleus contains 23 particles; since 11 of these are protons the remaining 12 are neutrons.

ISOTOPES

Atoms with the same number of protons but different number of neutrons will differ in weight but not in their chemical properties. Such atoms will, therefore, be isotopes of the same element.

Most chemical elements are a mixture of a number of isotopes. The isotopic composition of an element can be analysed by means of electrical

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(399)

and magnetic fields, and in this way the number, weight and abundance of the isotopes can be determined. Some elements, usually those with an odd atomic number, like fluorine, sodium, phosphorus, or iodine, consist of one

CONSTITUENTS OF ATOM

		MASS (IN ATOMIC WEIGHT UNITS)	CHARGE
IN NUCLEUS	PROTONS	1	+
	NEUTRONS	1	0
IN OUTER ORBITS	ELECTRONS	$\frac{1}{1836}$	-

FIG. 1.—The constitution of an atom.

isotope only. Other elements may contain 2, 3 or even 10 isotopes. The total number of stable isotopes which occur in nature and which are distributed among the 81 stable elements is 274, an average of about 3.5 per element.

Since isotopes of the same element differ from each other in atomic weight, when describing an isotope one must state both the symbol of the element and the mass number. The latter is usually given as a superscript before the symbol, e.g. ^{31}P , ^{127}I , ^{16}O , ^{17}O , ^{18}O . From this notation (and assuming a knowledge of the periodic table of the elements) the constitution of the atoms can be immediately inferred. Thus, phosphorus, being the 15th element, has a nucleus containing 15 protons and 16 neutrons; iodine (atomic number 53) consists of 53 protons and 74 neutrons. All the three isotopes of oxygen (atomic number 8) have 8 protons in their nuclei, but the number of neutrons is 8, 9 and 10 respectively.

RADIOACTIVE ISOTOPES

The 274 isotopes referred to above are stable ones; this means that unless interfered with their nuclei remain unchanged for an infinitely long time. In addition to these, however, there exist in nature, or can be produced artificially, a number of isotopes which are unstable. The nuclei of such isotopes disintegrate spontaneously in the course of time. Such a disintegration usually produces only a small change in the structure of the nucleus, but as a result of this a new isotope is formed, and at the same time some radiation is emitted. Hence the name 'radioactive' applied to such isotopes.

The lack of stability of such isotopes follows from the composition of their nuclei. In order to confine the particles in the tiny space of the nucleus, the protons and the neutrons must act on each other with very strong attractive forces. On the other hand, the protons being positively charged repel each other. The outcome of this is that only for certain combinations of protons and neutrons is the resulting force such as to keep the nucleus

together. If the proportion of neutrons and protons is changed the repulsive force may predominate and the nucleus will tend to break up and change over into a stable form.

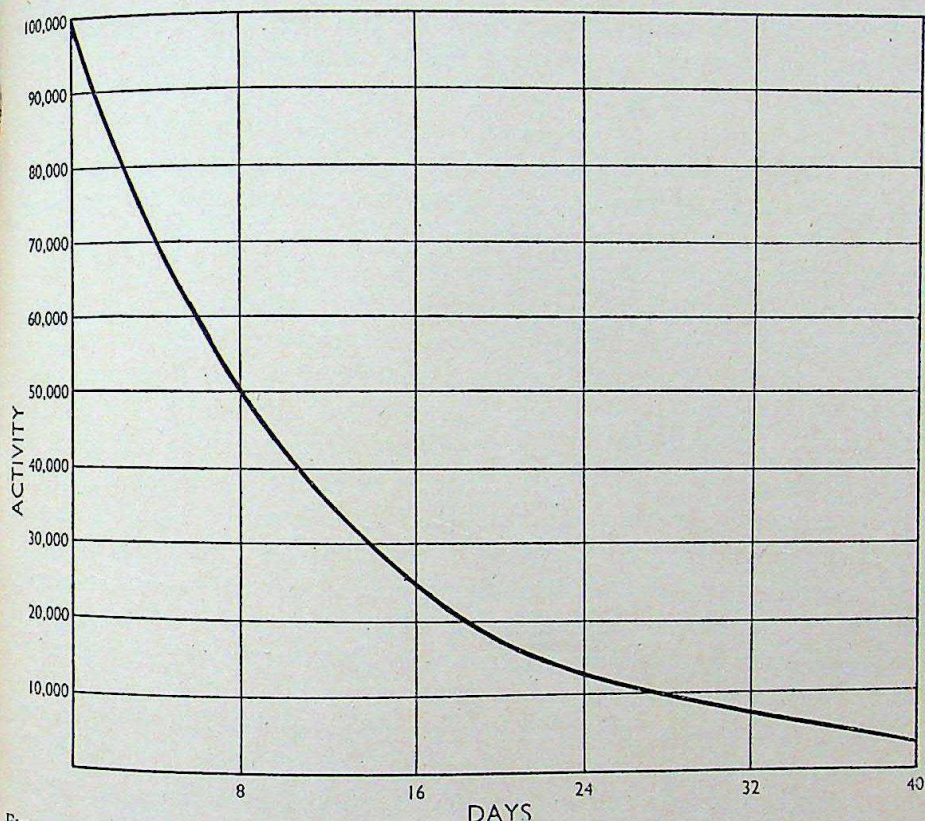


FIG. 2.—Rate of decay of a radioactive substance initially containing 100,000 radioactive atoms, and with a half-life of 8 days.

The break-up of a radioactive nucleus does not take place instantaneously. In a given radioactive substance some nuclei break up in a very short time, but others may exist for a very long time. It is a process governed by chance, but if the substance contains a very large number of unstable atoms a simple statistical law is observed, namely, that the same fraction of all the radioactive atoms present in the substance breaks up in equal intervals of time. The quantity which is usually employed to characterize the rate of decay is the so-called half-life, the period of time in which half of the radioactive atoms in the substance decay. If we consider, for example, a substance with a half-life of 8 days and containing initially 100,000 radioactive atoms, then after 8 days 50,000 atoms will be left; after 16 days 25,000; after 24 days 12,500, and so on. The graph in fig. 2 shows the rate of decay of such a substance as a function of time.

Since a radioactive substance is detected by the radiations emitted, and this depends upon the number of atoms breaking up, it is usual to measure

the strength of a radioactive substance in terms of the number of disintegrations per second, or activity. The unit of activity is called the curie; it is nearly the activity of 1 gramme of radium and is equal to the quantity of a radioactive substance in which 37,000 million nuclei break up every second. In practice smaller units are employed, i.e. the millicurie (one-thousandth of a curie) and the microcurie (one-millionth of a curie).

α -, β -, AND γ -RAYS

In most cases the break-up of an unstable nucleus consists of a change of a neutron into a proton, or vice versa. These two particles may be considered to be different states of the same particle of matter. The actual process of transformation is complicated and not yet well understood, but it is known that eventually it leads to the production of an electron. Thus, when a neutron changes into a proton, an electron is produced and is immediately emitted from the nucleus. If a proton is transformed into a neutron an electron with a positive charge, a positron, is produced and emitted. The emission of electrons, or β -rays, as they are called, can be detected by means of various instruments, and it is through the observation of such radiation that radioactivity is measured. β -rays are usually emitted from an unstable nucleus with some energy and since they have a very small mass, they start off with a great velocity which enables them to penetrate through some thickness of matter: i.e. a few millimetres of tissue. The energy of nuclear radiations is measured in units of million electron volts (MeV); the higher the energy the greater the penetration.

Not all of the energy available in an unstable nucleus is taken up by the emitted particles. Often some energy is left over and is subsequently emitted in the form of a pure radiation, identical in nature with x-rays. These radiations are called γ -rays and are much more penetrating than β -rays; they can pass through many centimetres of tissue.

In the heaviest elements yet another mode of decay, by the emission of α -particles, is observed. α -particles are nuclei of atoms of helium. Being much heavier than β -rays they can penetrate only through a very small thickness; a thin sheet of paper will stop them completely.

As in the case of stable isotopes each radioactive isotope is denoted by its atomic number and mass number; in addition, however, they are characterized by their half-life, type of emitted radiation and its energy.

The phenomenon of radioactivity was first discovered in the heaviest elements which occur in nature: e.g. uranium, thorium, radium. Later, however, it became possible to transform ordinary atoms into radioactive ones. This can be done either by the use of atom-smashing machines, in which charged particles are accelerated to very high energies and then employed to bombard and break up nuclei; or by means of nuclear reactors in which neutrons are used in a similar way. In addition, the complete break-up, or fission, of uranium nuclei leads to the production of a large number of radioactive isotopes.

Altogether, it has now been possible to produce over 800 radioactive isotopes, about three times more than the number of stable isotopes. There is now at least one radioactive isotope of every chemical element.

THE SIGNIFICANCE OF RADIOACTIVE ISOTOPES IN MEDICINE

The great importance of radioactive isotopes for medical and biological work arises from the fact that the radioactive isotope is chemically and biologically identical with the stable isotope, but the possession of radioactivity labels it, making possible its detection by observing the radiations

Isotope	Symbol	Half-life	Radiations emitted	Energy of β -rays (MeV)	Energy of γ -rays (MeV)
Tritium	^3T	12.26 years	β	0.0176	—
Carbon-14	^{14}C	5,900 years	β	0.155	—
Sodium-24	^{24}Na	15.06 hours	β, γ	1.400	1.38, 2.75
Phosphorus-32	^{32}P	14.30 days	β	1.711	—
Sulphur-35	^{35}S	87.1 days	β	0.167	—
Potassium-42	^{42}K	12.5 hours	β, γ	3.54	1.53
Calcium-45	^{45}Ca	164 days	β	0.25	—
Chromium-51	^{51}Cr	27.8 days	γ	—	0.325
Iron-59	^{59}Fe	45 days	β, γ	0.46	1.1, 1.3
Cobalt-60	^{60}Co	5.27 years	β, γ	0.306	1.17, 1.33
Arsenic-76	^{76}As	26.5 hours	β, γ	2.97	0.55—2.05
Bromine-82	^{82}Br	35.7 hours	β, γ	0.46	0.5—1.5
Rubidium-86	^{86}Rb	18.6 days	β, γ	1.79	0.53, 1.08
Strontium-90	^{90}Sr	27.7 years	β	0.61	—
Yttrium-90	^{90}Y	64.8 hours	β	2.26	—
Ruthenium-106	^{106}Ru	1.0 year	β	0.04	—
Iodine-131	^{131}I	8.05 days	β, γ	0.61	0.28, 0.36
Xenon-133	^{133}Xe	5.27 days	β, γ	0.34	0.081
Cesium-137	^{137}Cs	30 years	β, γ	0.52	0.67
Cerium-144	^{144}Ce	290 days	β, γ	0.327	0.03—0.14
Thulium-170	^{170}Tm	127 days	β, γ	0.95	0.084
Tantalum-182	^{182}Ta	111 days	β, γ	0.51	0.07—1.22
Gold-198	^{198}Au	2.70 days	β, γ	0.96	0.41

TABLE I.—Some radioactive isotopes used in medicine and biology.

emitted. The sensitivity of detecting instruments, such as the Geiger counter or scintillation counter, is so great that it is possible to detect by these means a quantity of matter millions of times smaller than that detectable by any other method.

For medical purposes, only a small fraction of all the radioactive isotopes can be used, since the suitability of an isotope depends upon its half-life, energy emitted, availability, and specific activity, as well as its biological properties. A list of isotopes most frequently used in medical and biological work is given in table I.

THE PREPARATION OF RADIOACTIVE ISOTOPES

BY HENRY SELIGMAN, Ph.D.

Head of Isotope Division, Atomic Energy Research Establishment, Harwell

ANY atom consists of a nucleus surrounded by electrons. The electrical charge of a nucleus of an atom defines the chemical element and the mass of the nucleus defines the isotope. Therefore if, for example, one has 79

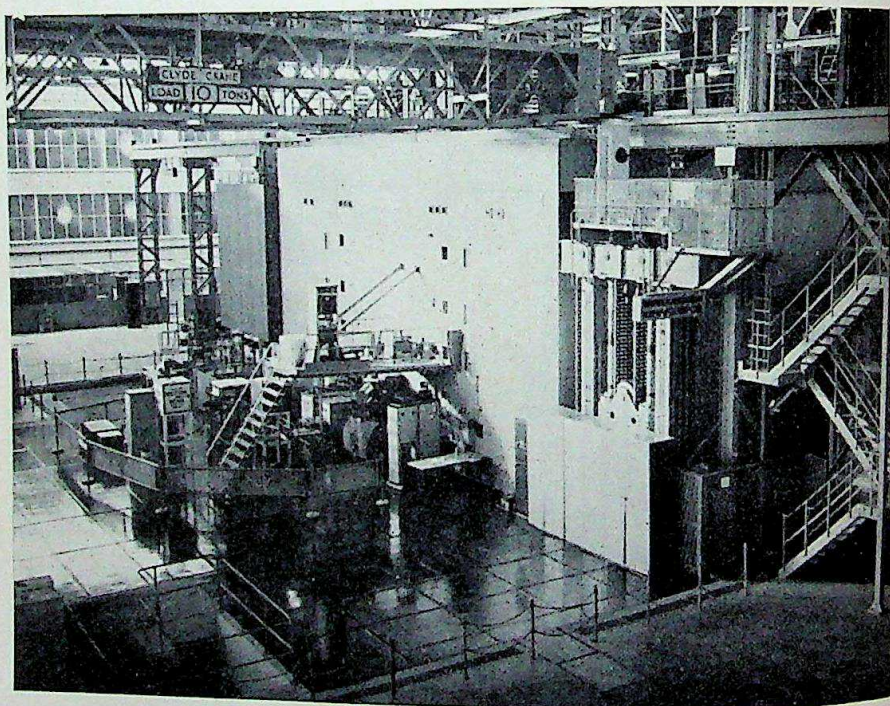


FIG. 1.—An atomic reactor.

electrical charges of a nucleus, the element is gold. The gold atom can have a weight of 197—this is the stable isotope of gold; but it can have different weights varying from 187 to 203, and all the other isotopes except the one with the weight of 197 are unstable—they are radioactive, which means that they emit radiations.

THE RATIONALE

To make a new isotope it is therefore necessary to change the weight of the nucleus; if, as a result of this change, a non-stable nucleus is obtained, this means that a radioactive variant has been formed. In other words, to make radioactive isotopes it is necessary to change the weight of normal stable nuclei. This can be done by bombardment of atoms with particles.

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They can be particles carrying electric charges, like protons or deuterons, or they can be neutral particles like the neutrons which are the unit of mass. The latter particle is especially suitable for bombardment as, because of its electrical neutrality, it can penetrate more easily into the nucleus. All that is necessary therefore is to bombard nuclei with particles which have a high enough energy to penetrate into the nucleus.

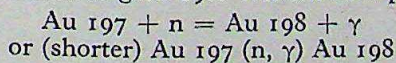
This can be done by producing, for example, protons or deuterons and bringing them to a high enough speed in a cyclotron or a similar machine, or it can be done by using atomic reactors (fig. 1) where we have a vast amount of neutrons which result from the fission, or splitting, of uranium.

CYCLOTRON OR ATOMIC REACTOR

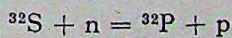
In a cyclotron, only one species of radioisotope can be made at a time and this is rather expensive, whilst in an atomic reactor many hundreds, or even thousands, of species of radioisotopes can be produced at the same time, but there is a fundamental difference between cyclotron- and reactor- produced radioactive materials. Electrically charged particles, as used in cyclotrons and incorporated into the nucleus, always change the target element. Neutron bombardment, however,

as done in an atomic reactor, normally does not necessarily change the target element.

If we have, for example, gold which is stable gold with the weight of 197, and it undergoes bombardment with neutrons in a reactor, we shall obtain gold with one unit heavier as a result, which is gold-198. Written in a physicist's language:—



There are many exceptions, where a neutron bombardment can change an element; this will always happen when an electrically charged particle is thrown out of the nucleus. One such example is the production of radioactive phosphorus from sulphur:—



There is still a number of isotopes which are made more easily with an electric machine. For example, the long-lived sodium-22 can be much more conveniently produced in a cyclotron, whilst the short-lived sodium-24 is best produced in an atomic reactor, but the reactor-produced materials are generally much cheaper. It is therefore not surprising that more than 99 per cent. of the shipments of radioactive materials going out are radio-

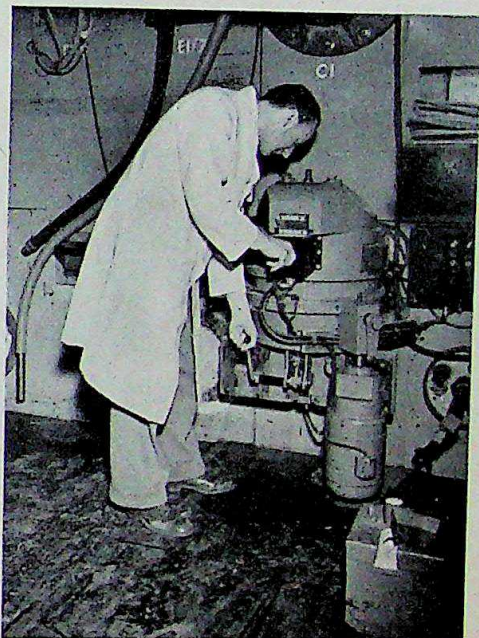


FIG. 2.—Placing small aluminium cans, containing target material, in an atomic reactor.

active materials produced exclusively in atomic reactors. For this reason, only atomic-reactor-produced isotopes will be discussed in this article.

THE TECHNIQUE

In order to make an irradiation we have to choose first the proper target material. Usually this is not a compound or a big molecule because the radiation itself is destroying chemical bonds and decomposing materials. For this reason chemically simple target materials are usually used. These may be pure metals or oxides of metals, but there are exceptions to this rule.

The irradiation time depends upon a number of physical data: e.g. the half-life, the cross-section and the neutron flux.

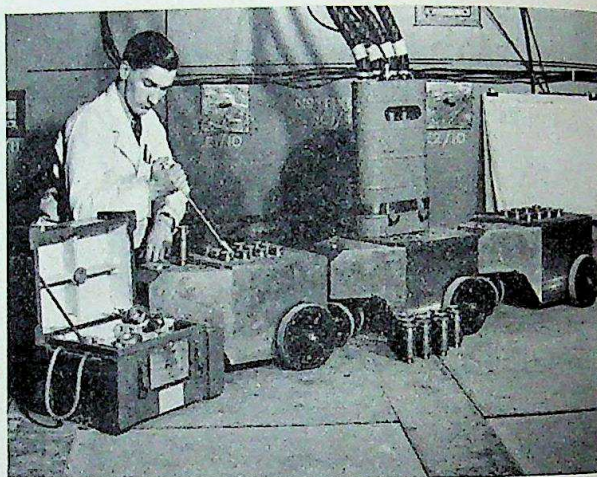


FIG. 3.—Removing radioactive material from atomic reactor by remote control.

The place in the reactor where the irradiation should take place has to be decided. This place varies according to the speed of neutrons desired, as in many cases the reactions are influenced by this. For example, sulphur in a slow neutron flux will give radioactive sulphur but the same element bombarded by fast neutrons will give radioactive phosphorus. Also some material which may be influenced by high temperatures will have to be put in a specially low neutron flux where the temperatures are usually lower or special cooling arrangements will have to be made.

The target materials have to be weighed and are usually put into small aluminium cans which are then inserted into an atomic reactor. This can be done even while the pile is running (fig. 2). After a certain time this material is removed by remote control (fig. 3) and transferred to the handling bay. Here the radioactivity is checked for its strength and the material is then loaded into transport containers. Some materials can then be used directly and are shipped from Harwell. These are, for example, radioactive sodium in the form of a salt; cobalt in the form of wire, or little cylinders; or gold in the form of grains for insertion into tissue.

CHEMICAL PROCESSING

Most materials, however, have to be chemically processed. Sometimes the radioisotope has to be separated; it has to be put into another chemical compound, standardized and often sterilized. Practically all chemical work of this nature is done by the Radiochemical Centre at Amersham which is a part of the Atomic Energy Research Establishment. The Radiochemical

Centre receives irradiated material from Harwell for chemical processing; the most important medical isotopes prepared at Amersham are iodine-132 which is prepared either by extraction from fission products or, as in the case at Amersham, by separation from a parent which is radioactive tellurium-132 (fig. 4). Another one is phosphorus-32 which has to be

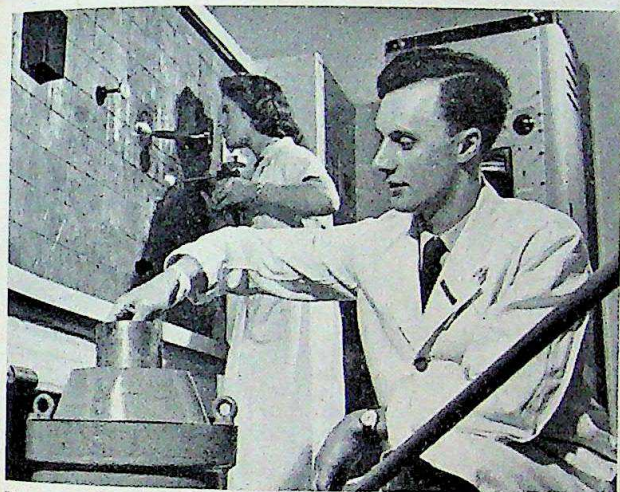


FIG. 4.—Operating a plant for the extraction of iodine-131.

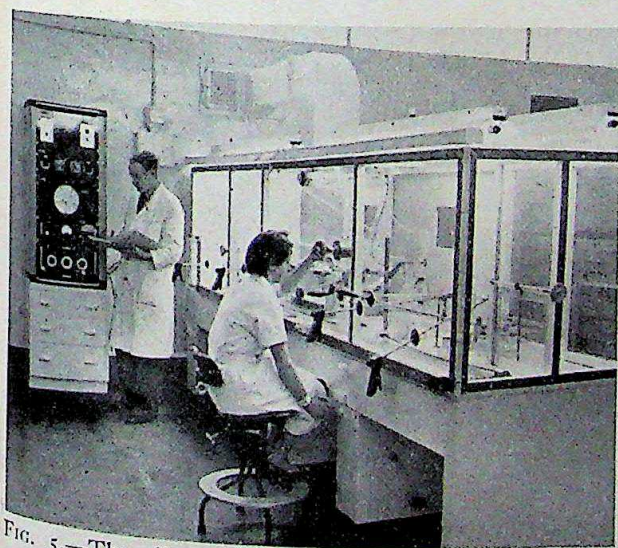


FIG. 5.—The dispensary at the Radiochemical Centre, Amersham, for beta-emitting isotopes.

chemically separated from irradiated sulphur. After these chemical separations have been done by remote control the activity of the solutions has to be assessed and they have to be checked chemically and eventually the material has to be dispensed (fig. 5) and some of it has to be sterilized afterwards.

Radioactive materials, such as iodine or phosphorus, which are separated chemically from other elements, are usually designated carrier-free, which means that practically all the atoms of the material are radioactive—a fact which can never be quite achieved practically. These materials have therefore a very high specific activity (activity per gramme): an extremely important factor in quite a number of applications.

MEDICAL RADIOACTIVE ISOTOPES

Many additional preparations of radioactive materials are made for the medical profession. For example, chromium-51 or iron-59 produced in the right form is used for certain blood determinations. Colloidal gold and gold

in the form of grains are used for malignant disease. A number of active materials whose radiations are not very penetrating, beta-active materials, are produced in special forms, some of them for ophthalmic applications (fig. 6), others for surface treatment of lesions. Radioactive materials such as phosphorus-32, strontium-90, cerium-144 and ruthenium-106 are being used in special applicators where the material may be put into certain plastics or into metal foil in order to make its use safe. It is always an important fact, which has to be verified, that material which is to be used from the outside is so safe that no loose radioactivity can



FIG. 6—Method of supplying radioactive isotopes for ophthalmic use.

come into the body and this is achieved by incorporating the radioactive material safely into plastics or metal foils. For biochemical work many organic compounds have been synthesized at the Radiochemical Centre; these are generally used as tracers.

More recently very big sources of radioactive materials have been produced and are being used in therapy in this country. For example, large sources of cobalt-60 produced in atomic reactors are being used for teletherapy treatment, and only a few months ago the first teletherapy source made from atomic fission products (waste products) was prepared in this country by the Industrial Group of the Atomic Energy Authority. In this case radioactive caesium-137 had been isolated from used atomic fuel rods. It is hoped that in the future this material will become available in bigger quantities and that many more hospitals will be able to obtain such a source.

CONCLUSION

In Great Britain we have the closely coordinated services between the Isotope Division at Harwell, the Radiochemical Centre at Amersham, and the Windscale Works of the Industrial Group, all belonging to the Atomic Energy Authority, and we are in the happy position to have available in this country a greater variety of radioactive materials than anywhere else in the world. Constantly we add to our lists new radioactive materials or old ones but in different form. It is not surprising therefore that Great Britain is by far the greatest isotope exporter in the world today, some fifty countries obtaining their isotopes from this country.

THE ACTION OF RADIOACTIVE ISOTOPES

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RADIOACTIVE atoms may be encountered clinically within the body in three different connexions: in diagnosis, in therapy and in occupational medicine.

EMISSIONS FROM RADIOACTIVE ATOMS

The unstable radioactive atom disintegrates and emits some form of radiation in the attempt of the atomic nucleus to stabilize itself. Many of the naturally radioactive elements of high atomic number (such as uranium, thorium, radium) emit α -particles, nuclei of helium atoms. Others, and many of the artificially produced radioactive isotopes of stable elements, give off β -particles. In either case (α - or β -particle-emission) an electromagnetic radiation—a γ -ray—may be associated with the particle. These radiations, particulate and electromagnetic, have this in common: they cause ionization within the material in which they are absorbed—air, water or tissue. They are thus classed among the ionizing radiations and are to be differentiated from visible and ultra-violet light and other non-ionizing radiations.

The α -particle, a massive thing comparatively speaking and having a positive electric charge, cannot travel far. Its path is limited to 12 inches (30.5 cm.) or so in air and to a few tens of microns in water or tissue. As it expends its kinetic energy it causes densely packed ionizations along its short path. The β -particle, an electron, is several thousand times less massive and travels farther, up to a centimetre in tissue; but the ionizations along its path are relatively scanty until near the end of its track. γ -radiation can be considered as similar in many ways to particulate radiation, each quantum on absorption in a medium leads to the ejection of an electron from the molecule in which it is absorbed. It differs in that it is much more penetrating and even soft γ -rays and the physically similar x-rays can travel long distances in tissue before giving up their energy, whilst hard highly energetic γ -rays can penetrate right through the body.

TRACER STUDIES FOR DIAGNOSIS

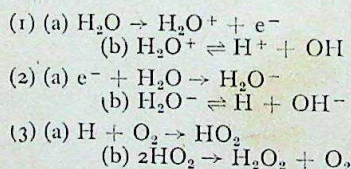
In diagnosis one makes use of the fact of the disintegration, and the liberated energy—particulate or electromagnetic—is picked up by an appropriate device: e.g. ion chamber, Geiger counter, scintillation counter. One can thus determine such parameters as circulation times, efficacy of uptake and utilization of elements and radicals by the so-called 'tracer method'. It is particularly important that the radioactive material should be present in no

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more than the trace or minimal amount necessary for the exercise. Even in chemical reactions *in vitro* too great a concentration of radioactivity can alter the properties of reactants. Biological systems *in vivo* are still more sensitive so that misuse of radioactivity is not only misleading but dangerous.

PHYSICAL AND PHYSICOCHEMICAL EFFECTS OF IONIZATION
Under suitable conditions this damaging action can be utilized for therapeutic purposes. The damage is due to the process of ionization with probably additional effect from molecular excitation such as occurs under the influence of ultra-violet radiation. The ionization may act by direct or indirect effect. The direct action is thought to be mainly on large protein molecules which, when electrons are ejected, undergo internal rearrangement and are denatured as a consequence. If they are essential proteins and not replaceable, as may be the case with certain nuclear materials (e.g. a gene controlling a cytoplasmic enzyme), the cell is seriously embarrassed. The indirect action is probably mainly through the ionization of the water molecule—the most abundant molecule in tissue. Several reactions are known to occur:—



The positively charged water molecule left when an electron is ejected under the influence of radiation dissociates to give the normal hydrogen ion and the abnormal hydroxyl radical. This latter is a highly active oxidizing agent. The hydrogen radical formed in equation (2) is equally a highly active reducing agent but in the presence of molecular oxygen can form oxidizing substances as in equation (3). These reactions of oxidation or reduction, occurring focally in cells, in chromosomes or other sensitive targets, could also cause irreparable damage.

These reactions, direct or indirect, will occur in the immediate environment of the ionization or at variable distances from the radioactive atom, depending upon which particular isotope it is of which particular atom. An α -emitting isotope of, say, radium will have this extremely dense ionization in a track of some 30μ from the disintegrating atom. The damaging effect resulting from this concentration of ionization is about ten times greater per unit of energy delivered per unit mass (i.e. physical dose) than with β -radiation. Whilst β -particles and x- and γ -rays have about the same biological efficiency for equal physical dose, the greater range of the γ -rays leads to the physical energy being distributed more widely than with β -rays.

BIOLOGICAL FACTORS OF LOCALIZATION

In addition to these physical factors one has to consider the biological factor of localization of a particular atom. Radioactive sodium (^{24}Na) for

instance) would be expected to distribute itself within the body uniformly in extra-cellular water. Practically all of the β -rays of this particular nuclide would be effective in giving whole-body-irradiation. The γ -rays, however, though coming from the same uniformly distributed atoms, would be lost to a considerable extent outside the body. Radioactive iodine, ^{131}I , is also a $\beta+\gamma$ emitter, but the iodine is highly concentrated in the thyroid, so that the β -rays there give an intense irradiation and the γ -rays a more widely distributed less intense dose. Where high biological concentration is combined with high biological effectiveness (α -rays), then one gets the maximum of local effect.

UTILIZATION OF IONIZATION FOR THERAPY

Only in a few instances has biological concentration been suitable for therapeutic purposes. Iodine and the thyroid is the most impressive instance. Phosphate and actively dividing cells utilizing phosphate for desoxy-ribosenucleic acid formation, e.g. the bone marrow in polycythæmia vera, is another.

OCCUPATIONAL HAZARDS

A few occupations in the past were concerned with the mining, processing or use of the naturally radioactive materials. Already there is an important chapter in the history of industrial medicine dealing with the attendant disorders from the intake of these substances into the body. Inhalation of radioactive ores has led, when the exposure was long, as in the Schneeberg and Joachimstal mines, to carcinoma of the lung. Ingestion of radium, mesothorium, and radiothorium by those who first refined these materials or used them in the luminizing industry has now long been known to cause, depending upon dose, subacute refractory or aplastic anæmia, necrosis of bone and osteosarcoma. As a consequence of these earlier mistakes it has been possible to assess the risks at the present day and in future occupations involving the production and use of artificially produced radioactive materials.

PATHOLOGICAL ASPECTS

From the foregoing it can be concluded what is the pathological effect of excess irradiation. It is necessary to stress that we can only be certain about the effects of the excess. There is in all circumstances natural irradiation of the body both from without and within. The earth itself contains everywhere traces of the naturally radioactive materials, uranium and thorium and their decay products. In some geological formations, especially in areas of granitic rock, the concentration may be several times that of the terrestrial average. In a few restricted localities the concentration may be high enough to make mining profitable. Other naturally radioactive materials are potassium and carbon. Each of these elements, which are essential constituents of tissue, has a radioactive isotope, ^{40}K and ^{14}C respectively, which is present in minute amount together with the more abundant stable isotopes, ^{39}K , ^{41}K , ^{12}C and ^{13}C . Moreover, we receive

irradiation from cosmic sources. How far these radiations are with or without effect on living tissue is at the moment still a matter of speculation.

If we consider the effect of excess radiation we deduce from the introduction that irradiation can lead to death, either of individual cells or tissue or the whole organism. Some tissues are much more vulnerable than others. As a general law it can be said that tissues in a constant state of reproduction are those which are radiosensitive. Thus hæmopoietic tissue, both bone marrow and lymphatic tissue, is readily destroyed; the mucosa of the gut is if anything even more sensitive and so is the male germinal epithelium, whilst skin is rather less affected. In fact the biological process which apparently is most vulnerable is that of cell reproduction. Mitotic division is the method by which this is generally considered to occur, so that much research has been devoted to the investigation of the effects of radiation thereon. Nevertheless, interference with mitosis should not be rated as the sole cause of death of cells. The small lymphocyte is usually thought to be an end-cell and not to undergo mitotic division, yet it is extremely radiosensitive. Following irradiation its nucleus rapidly becomes pyknotic and cytolysis supervenes. Presumably the radiosensitive ovum dies in similar fashion. This process of cell death without division can be seen to occur in other tissues where cell division by mitosis is actively going on: the tubule of the testis is a case in point. It may well be that the really sensitive process is not the turnover of cells *per se*, but the turnover of chemical material within the nucleus. Thus, desoxyribosenucleoprotein has not only been elaborated at some point in time in interphase before cell division, but certainly in the case of the radiosensitive small lymphocyte is being replaced even though the cell is not expected, according to conventional theory, to divide again.

The effects of irradiation on the process of mitosis are readily observed after doses which are known to produce significant effects on the tissue. Following a single dose of x- or γ -rays of about 50r the mitotic rate will be slowed for a while. Following this there may be a rebound phenomenon, the rate increasing to a figure above the average normal. There may thus be phases of depression and apparent stimulation following a short-lived irradiation. With continuous irradiation, such as will occur with internal irradiation from most internally deposited radioactive materials, there will be a depression of mitotic rate, but if the dose is not too great adaptation may occur with a return towards normal in spite of the continuing irradiation. In therapy with radiation or with radioactive isotopes the aim, certainly in cases of cancer, is a concentration of radiation which will not only depress the rate of mitosis but which will cause mechanical damage of the cell-productive works.

The proper progression of events in mitosis is dependent upon the orderly arrangement on the spindle of the divided chromosomes which are to be drawn to the respective daughter cells. The ionizing particles passing through the resting nucleus result, either by direct ionization or

indirectly by physicochemical action, in fractures of the chromosomal material. Any such fracture which does not spontaneously heal results in disordered action at the next mitosis. Daughter cells formed are unbalanced, compared with the normal, in their complement of chromosomes. Subsequent mitotic divisions are then impossible. This is certainly true with normal tissues. Unhappily, malignant growths are not only characterized by a high rate of turnover of cells, which should make them radiosensitive, but often have an abnormal complement of chromosomes: as if, in virtue of their state of malignancy, they had become adapted to a state of imbalance so that a further disorganization by radiation has a smaller than expected effect.

RELATIONSHIP BETWEEN DOSE AND EFFECT

Between most doses of radiation—over and above the normal background—and biological effect there is a relation comparable with the usual response to a noxious substance such as a chemical or bacterial agent. The graph of effect upon dose is sigmoid in shape. Normally one finds so great a variation amongst individuals that it is usual to graph effect versus the logarithm of the dose in order the better to demonstrate the sigmoid form. With radiation, however, there is much more uniformity of response and the relationship is seen when effect is plotted against dose directly. For practically all the biological effects of radiation this expression holds good. There is, however, a classical exception. Ionizing radiation not only produces somatic effects but genetic effects. The rate of gene mutation is increased on exposure of the germ cell to such radiations. The plot of the increase in mutation rate upon dose is a linear function. In the jargon of radiobiological theory it is a 'single hit' effect. One hit on the gene with an ionization leads to the change, whereas to produce the sigmoid shape of graph multiple, more or less simultaneous, events are required.

INDUCTION OF CANCER

It is possible that the induction of malignant change is a similar phenomenon in a somatic cell to genetic mutation in a germ cell. In fact, one of the theories of carcinogenesis which waxes and wanes in popularity involves the 'somatic mutation'. Possibly the most suggestive evidence in its support is the observation of the Medical Research Council's committee in 'The Hazards to Man of Nuclear and Allied Radiation' of a more or less linear relationship of the incidence of leukæmia following radiation with dose. Here the time factor over which the irradiation was given seemed of little importance. In most experimental approaches with experimental animals, however, the dose rate as well as the total dose has been a factor of importance in the production or failed production of cancer. Prolongation of the dose in time has usually facilitated induction of new growth. In terms of radioactive materials deposited internally this means that one should beware of those with long effective half-lives in the body and those which have a high focal or tissue concentration.

SOME USES OF ISOTOPES IN RESEARCH

WITH SPECIAL REFERENCE TO TURNOVER STUDIES

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THE basic principle on which the use of isotopes rests in all biological research is the simple fact that the living cell cannot distinguish between the various isotopes of the same element. This statement has a wider meaning in that the cells cannot differentiate even between substances containing the naturally occurring elements and substances containing, in one or more chemical groupings, artificially produced radioactive isotopes of these elements. The same applies to a compound in which the proportion of one of the naturally occurring, but rare, isotopes has artificially been raised. For example it is possible to prepare the amino-acid glycine, $\text{CH}_2\text{NH}_2\text{COOH}$, so that 10 to 50 per cent. (or even more) of all its nitrogen consists of the rare, naturally occurring and non-radioactive heavy isotope ^{15}N instead of the normal 0.38 per cent. Preparations of glycine can also be made in which either of its carbon atoms contains a high proportion of radiocarbon ($^{14}\text{CH}_2\text{NH}_2\text{CO}_2\text{H}$ or $\text{CH}_2\text{NH}_2\text{.}^{14}\text{CO}_2\text{H}$). So far as is known, these variously labelled forms of this amino-acid are treated by animals as their natural counterpart.

'TRACER EXPERIMENTS' IN NATURE

In all natural waters there are two isotopic forms of hydrogen: one has an atomic weight, in round figures, of one (hydrogen=protium, ^1H) and the other of two (deuterium, ^2H or D). Of all the hydrogen in these waters 99.98 per cent. is protium and only 0.02 per cent. is accounted for as deuterium. When the hydrogen contained in organic substances of living matter is analysed, it is found again that 99.98 per cent. consists of ^1H and 0.02 per cent. of ^2H . The same principle applies generally to other elements of biological importance also: namely, that the various isotopes of these occur in living organisms in the same proportion as found in their inanimate surroundings. Clearly, if cells were to use preferentially either the lighter or the heavier isotope of any one element in building up their constituents the proportions of these isotopes in living matter would differ from those found in the inanimate world surrounding us. It is immaterial in this respect whether an isotope is stable or radioactive.

One of the radioactive isotopes of carbon, ^{14}C , has a half-life of 6000 years and occurs naturally in minute amounts. This radioactive carbon, in the

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form of CO_2 , has been 'fixed' through thousands of years by plants by photosynthesis into their organic constituents; animals in turn acquired such ^{14}C mostly by eating the plants. Of course, when the plants or animals die any further accumulation of the ^{14}C ceases, but in such dead remains of plants and animals, or articles manufactured from plant and animal products, that 'survived' the ravages of many centuries the ^{14}C is still detectable. Since, however, ^{14}C decays with a half-life of 6000 years, the amount of this isotope found now in these dead remains depends upon the age of the articles. So constant has been the amount of $^{14}\text{CO}_2$ in the atmosphere and its inclusion into living matter that, by careful determination of the proportion of radiocarbon in the carbon of ancient articles, it is possible to calculate their age as far back as 30,000 to 40,000 years with an accuracy of about ± 200 years. This method is known as 'carbon dating'.

The two examples quoted are in effect 'tracer experiments' provided by nature. For purposes of laboratory experimentation we have now a wide variety of isotopes to choose from, each suited for a particular purpose. Returning, briefly, to the example of incorporation of naturally occurring $^{14}\text{CO}_2$ by plants into their constituents in the course of photosynthesis, an experiment may easily be devised by putting a plant into an atmosphere in which the concentration of $^{14}\text{CO}_2$ has artificially been raised and then exposing the plant to light for varying intervals ranging from a few seconds to minutes or hours. By an analysis of the cell constituents for their content of radiocarbon at these intervals a 'pathway' of the CO_2 in the photosynthesis of carbohydrate, for example, may be described. This has in fact been achieved and the various metabolic events in this fundamental process of life are now known in great detail through the use of ^{14}C .

In this number of *The Practitioner* various diagnostic and therapeutic uses of radioactive isotopes are also described. Most of these applications depend upon the incorporation of a suitable isotope, administered to a patient in a relatively simple chemical form, into some more complex tissue constituent, such as the formation of radioactive thyroxine from K^{131}I or the formation of many radioactive organo-phosphorus compounds from inorganic $^{32}\text{PO}_4$. All these incorporations depend upon the metabolic activities of the cells and it is in the study of these metabolic processes that isotopes have proved of greatest value.

REGENERATION OF BODY CONSTITUENTS

The first most important discovery made with the aid of isotopic tracers was the realization that the constituents of most tissue cells are in a continuous state of flux, undergoing degradation and resynthesis (Schoenheimer, 1941). In an adult animal, whose body weight is kept constant, these two processes, degradation and resynthesis, exactly balance and are responsible for the constant composition of the tissues. Behind this seeming constancy there lies a process of continuous regeneration, which is referred to generally as the turnover of the various body substances. In this connexion two

terms must be defined: (a) turnover time and (b) turnover rate. The *turnover time* of a tissue substance may be defined as the time required for the regeneration of an amount of the substance equal to that contained in the tissue or body fluid. This may vary from some minutes, as in the instance of some organic phosphorus compounds (adenosinediphosphate, adenosine-triphosphate), to several days as in the instance of plasma proteins. The *turnover rate*, of course, can be calculated from (a) and is defined as the amount of a substance that is renewed in a unit length of time. For example, the turnover rate of liver cholesterol in the rabbit is about 50 mg./day/100 g. liver (Popják and Beeckmans, 1950b). Since the rabbit's liver contains 200 to 300 mg. of cholesterol per 100 g., the turnover time of this substance in that organ is 4 to 6 days.

Measurement of either of these two parameters of body substances is of interest not only from a purely academic point of view, but may also be of practical value. Some of the clinical diagnostic uses of radioisotopes depend upon the changes of turnover rates of some body substances: e.g. the diagnosis of thyroid disorders with radioiodine hinges on the altered turnover of various iodine compounds in such diseases. Since the determination of turnover times and turnover rates of various substances often involves the use of isotopically labelled 'precursors', it will be necessary to discuss first what is meant by a precursor. A definition may be arrived at in the easiest way by considering briefly how the regeneration of the various substances in the body is achieved.

Much of our knowledge on this question was gained through the use of isotopes in various researches. It is now known that most biological systems, ranging from a single-cell organism to the vertebrates, manufacture their cell constituents from small molecules in preference to accepting large unchanged molecules from their food. In vertebrates this is achieved by the reassembly of the fragments into which the constituents of diet are usually broken down in the course of digestion, or in the course of metabolic processes occurring outside the digestive tract. The fragments into which the substances contained in the diet or within cells are broken down often provide not only combustible fuel for energy-yielding processes but also the primary building units from which larger molecules are synthesized. For example, fatty acids are broken down to acetic acid and they are also synthesized from acetic acid; furthermore, acetic acid is oxidized in the citric acid cycle and is a most important source of energy in the animal organism. Such a complete interchange of intermediates in the breakdown and synthesis of a substance, however, is not a general rule. Cholesterol is synthesized also from acetic acid but is not broken down to acetate but to bile acids. The protoporphyrin of hæmoglobin is synthesized from a pyrrole, porphobilinogen (Falk, Dresel and Rimington, 1953); the latter is derived from two molecules of δ -aminolaevulinic acid (Shemin and Russell, 1953; Neuberger and Scott, 1953) which in turn is made from the condensation of succinic acid with glycine. In these examples acetic acid may be called the

precursor of both fatty acids and of cholesterol, and cholesterol the precursor of bile acids. Generally speaking the term precursor applies to any substance which can be shown to contribute either specific chemical groupings or its entire carbon skeleton in the formation of another. When the formation of a substance involves several steps, as in the above example of the biosynthesis of protoporphyrins, the substance immediately preceding the final product is called the 'immediate precursor'. Thus, succinate and glycine may be called precursors of porphyrin, but they are immediate precursors only of δ -aminolaevulinic acid.

METHODS OF MEASURING TURNOVER RATES AND TIMES IN BIOLOGICAL SYSTEMS IN A STEADY STATE

The methods to be described in a simplified manner may be applied to systems in which the rate of synthesis of a substance is equal to its rate of degradation; such a system is said to be in a steady state or dynamic equilibrium.

METHODS DEPENDING ON THE ADMINISTRATION OF A LABELLED PRECURSOR IN A SINGLE DOSE

The most frequently employed method for measuring the turnover of a substance depends upon the use of its labelled precursor. For example, in order to measure the turnover of fatty acids or that of cholesterol in the tissues we might inject into an animal acetate labelled either with tritium ($C^3H_3.CO_2H$) or with a carbon isotope, e.g. ^{14}C ($^{14}CH_3.CO_2H$, or $CH_3. ^{14}CO_2H$).

Let us assume a hypothetical system in which substance A occurring in the blood is the immediate precursor of substance B in one of the organs and B the immediate precursor of compound C. If a small amount of substance A, suitably labelled with an isotope, is injected intravenously, it will mix with the same substance present in the blood in an unlabelled form. If frequent samples were taken and substance A isolated, it would be found that its specific activity (or its isotope content/unit weight) would vary with time as shown in fig. 1 (curve A). The rate of fall of the isotope content of the blood will depend upon the rate at which substance A is being transferred from the blood to all the tissues and on the rate at which similar, but unlabelled, molecules pass from the tissues into the blood. In other words, the rate of change in the isotope content of the blood will be a function of the turnover of substance A.

Without going into the mathematical reasoning of the calculations, the turnover time t_t of substance A in the blood may be calculated by the formula $t_t = t_{\frac{1}{2}} \log_e 2 = t_{\frac{1}{2}} / 0.693$; where $t_{\frac{1}{2}}$ is the half-life of the substance and is defined as the time required for its isotope content to fall to one-half of the initial value. If the total amount (W) of substance A in the circulating blood volume is known, the turnover rate is given by W/t_t .

If only the turnover time of substance A is required, it is not necessary to isolate substance A, but merely to measure at intervals the radioactivity

contained in a unit volume of blood provided there is no radioactive substance present other than A. The latter condition, however, usually does not prevail for very long after the injection, because, if substance A is an intermediate in metabolism, it will give rise to other labelled substances and these in turn will (or may) appear in the blood.

The change with time in the specific activity of compound B, whose immediate precursor is A, will be of the type shown in fig. 1 (curve B) and the specific activity:time curve of compound C, which is directly derived from substance B as shown by curve C. This type of relationship between the specific activity of the immediate precursor and its product was put forward on the basis of mathematical considerations by Zilversmit, Entenman and Fishler (1943a).

The curves in fig. 1 illustrate that the specific activity of the product, before its maximum had been reached, is always lower than that of its precursor; at the maximum it is equal to the specific activity of the precursor, and after the maximum, when it begins to decline exponentially, it is higher than the specific activity of the precursor. Zilversmit *et al.* (1943a) have shown that the turnover time of a substance may be calculated from the relationship between the specific activity:time curves of the precursor and of the product.

Referring to fig. 1, let the specific activity of compound C at time t_1 be S_1 and at time t_2 be S_2 . Then it can be shown that the turnover time, t_t of compound C is given by the shaded area, P, in fig. 1 divided by $(S_2 - S_1)$, i.e. $t_t = P/(S_2 - S_1)$. The area, P, is the area under curve B minus the area under curve C between the two chosen time limits of t_1 and t_2 .

It will be readily appreciated that several determinations are required in order to define each curve and that the precursor of the substance investigated must be known. Furthermore, the precursor must occur in the blood or tissues in amounts that will permit its isolation. These conditions severely limit the general usefulness of the method and it is not surprising that in relatively few investigations has it been made use of (e.g. Zilversmit, Entenman and Chaikoff, 1948; Popják and Muir, 1950).

The relationships just discussed can be used also to identify the as yet unknown immediate precursor of a substance. If, using the example given in fig. 1, it is observed that after the administration of labelled substance A only substance B, out of several others tested, is related to compound C

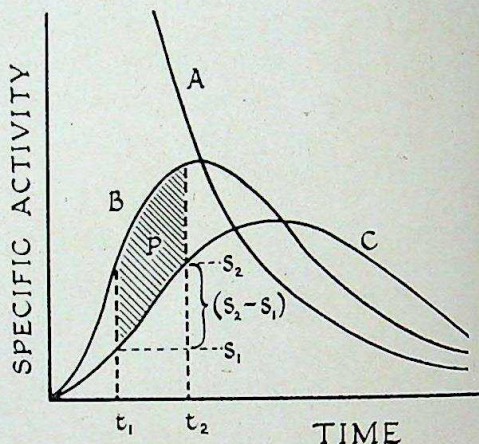


FIG. 1.—Relationship between the specific activities of precursor and product after the administration of a single dose of labelled precursor.

in the manner illustrated by curves B and C, it may be assumed that B is the immediate precursor of C. For example, Popják, Glascock and Folley (1952) found that after the injection of acetic acid labelled with ^{14}C in the carboxyl-carbon ($\text{CH}_3\text{.}^{14}\text{CO}_2\text{H}$) to a lactating animal the lactose in the milk and the glycerol of milk fat became labelled, in addition to the fatty acids.

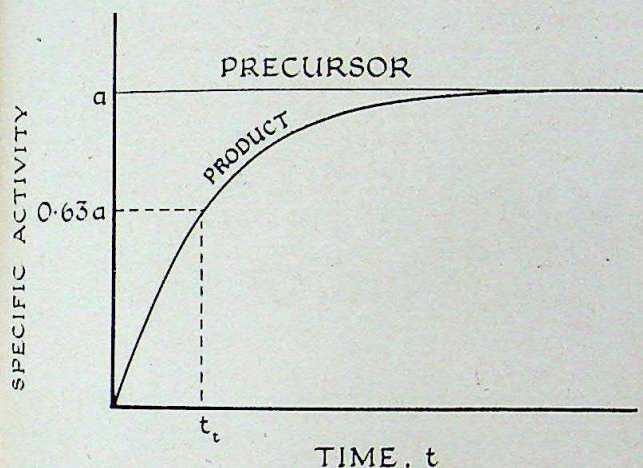


FIG. 2.—Relationship between the specific activity of a substance derived from a labelled precursor when the specific activity of the precursor is maintained constant in the body.

The specific activity: time curves of lactose and of glycerol were related to one another as curves B and C in fig. 1. Since there were good reasons for believing that the specific activity of the lactose represented also the specific activity of hexose that was metabolized in the mammary gland, it was concluded that the glycerol of milk-

fat was derived in the mammary gland from hexose.

A further comment is required here on the use of single doses of isotopically labelled precursors for the measurement of turnover rates. As we have seen, after the administration of a single dose of a labelled precursor, the specific activity of the substance derived from it will vary continuously with time. It is therefore rarely, if ever, possible to obtain quantitatively useful information regarding turnover rates from measurements made at one time interval after the administration of the labelled substance. Also, if substance A is converted into C through a series of intermediates and the immediate precursor of C is not known, then absolute values of turnover rates for C cannot be established. Nevertheless, the rate of incorporation of the label into C relative to the amounts of isotope present in A can give very useful data in certain types of investigation, as for example in deciding whether an experimental treatment alters the rate of metabolism of C or not.

METHODS DEPENDING ON THE CONTINUOUS ADMINISTRATION OF A LABELLED PRECURSOR

In another technical approach to the measurement of turnover times the labelled precursor is administered at frequent intervals in small doses, or continuously, for several hours or days, the aim being to maintain the specific activity of the precursor in the body at a constant level. In this instance the specific activity of a substance derived from the precursor will gradually rise in a manner shown in fig. 2.

Let the specific activity of the precursor in the body be a , constant, and that of its product at any time, t , be y . If the turnover time of the product is t_t , then it can be derived mathematically (Zilversmit *et al.*, 1943a) that its specific activity, y , will vary with time according to equation (1): $y = a(1 - e^{-t/t_t})$ (1) where e is the base of the natural logarithm. At turnover time $t = t_t$ and $y = a(1 - e^{-1}) = 0.63a$. In other words, at turnover time the ratio of the specific activity of the product to that of the precursor (y/a) will be 0.63. Equation (1) may be put into another form; at any $1/n$ -th fraction of the turnover time $t = t_t/n$ and we can write $y/a = (1 - e^{-1/n})$ (2). Since the ratio y/a can be determined at any time t , the value of n can be calculated from equation (2) and hence the turnover time is obtained by $t_t = nt$.

This type of experimental technique has much in its favour particularly when the precursor can be administered conveniently either in food or drinking water. The number of determinations required to obtain data for the calculations is much fewer than after the administration of a single dose of the labelled precursor. Theoretically one single determination should suffice provided one can be reasonably well satisfied that the specific activity of the precursor has in fact been maintained constant.

USE OF LABELLED WATER FOR MEASURING TURNOVER TIMES

A special case of this experimental approach is the use of either heavy water, D_2O (deuterium oxide), or of radioactive water, T_2O (tritium oxide), in the measurement of rates of synthesis of body constituents. In many biological syntheses the intermediates resulting from the condensation of small molecules are reduced with hydrogen. The best examples of this type of reductive syntheses are the formation of fatty acids and of cholesterol from acetic acid. The hydrogen donors for these reductive reactions are in rapid equilibrium with the hydrogen of body water. If therefore such syntheses occur in an environment containing labelled water (D_2O or T_2O) the hydrogen isotope will be incorporated into the newly formed molecules at every point where reduction occurs. It is particularly easy to maintain constant the concentration of either D_2O or T_2O in the body of a subject by first injecting an amount of saline, made up with a chosen concentration of the labelled water, in order to bring the concentration of, say, D_2O in the total body water to 1 per cent. and then to replace the drinking water with 1.5 per cent. D_2O . The concentration of D_2O in the body can be kept steady at about 1 per cent. level for days or weeks.

In the first extensive use of an isotope for metabolic investigations Schoenheimer and his colleagues (Schoenheimer, 1941) employed this very technique. The formulæ, (1) and (2), given in the previous section, however, cannot be applied without modification because the final concentration of the hydrogen isotope in the newly synthesized molecules will not be the same as in the body water but somewhat lower, depending upon the number of positions reduced in the molecule. For example, in the case of saturated fatty acids, when all the fat has been newly synthesized, the concentration of the hydrogen isotope will be only 50 per cent. of that found in body water (Schoenheimer, 1941); for cholesterol this value is 63 per cent. (Popják and Beeckmans, 1950b). In other words, the concentration of the

hydrogen isotope in each substance will tend to a maximum characteristic of that substance.

If the maximum isotope concentration attainable in a substance under these conditions and after prolonged maintenance on labelled water is i_m , then the isotope concentration, i , in the substance at any time, t , will be related to the turnover time, t_1 , according to equation (3): $i = i_m(1 - e^{-t/t_1})$ (3) from which the turnover time may be calculated as from equation (2). The only condition of this method is that i_m must be determined for each substance in experiments of long duration.

Fortunately this value is now available for substances for the study of which labelled water can be used (lipids and carbohydrates).

This method is also of interest because, with minor modifications, it can be used for the evaluation of both rates of synthesis and rates of degradation of substances in a biological system which is not in a steady state, for example in the growing embryo. Under conditions of growth synthesis must outstrip the degradative processes and therefore the concept of turnover cannot be applied; instead one must define both the rates of synthesis and rates of degradation. It was by the application of this method that Goldwater and Stetten (1947) measured the rate of synthesis and degradation of foetal glycogen and Popják and Beeckmans (1950a) evaluated the same parameters for foetal lipids. To illustrate the deviation from a steady state it may be of interest to mention that in the rat foetus on the 19th day of pregnancy 5 mg. of glycogen are synthesized per 1 g. body weight per day; of this, 3 mg. are degraded and 2 mg. deposited. In the liver of the rabbit foetus on the 28th day of gestation 1.64 mg. of cholesterol are synthesized and 0.82 mg. degraded, resulting in a net accumulation of 0.82 mg. Similar conditions must prevail also in tumours.

DETERMINATION OF TURNOVER RATE OF A SUBSTANCE IN BLOOD

The turnover rate of almost any of the constituents of the blood plasma can be determined if, instead of labelled precursor, the compound in question is introduced into the circulation in a labelled form. Since, according to the concept of the dynamic equilibrium of body constituents, the rate of appearance and rate of disappearance of a substance are equal in the 'steady state', the turnover rate can be measured from the rate of disappearance. In the first method described in this article and illustrated in fig. 1 the turnover time of precursor A in the blood was calculated on the basis of this principle from the half-life of compound A in the blood. The half-life of a metabolite, such as acetate, glucose or an amino-acid in the blood, is usually very short, and is measured in minutes. The half-life of larger molecules, such as lipids and proteins, is, however, much longer: several hours or days. It is often not feasible to extend the period of observation beyond a few hours and therefore turnover rates must be calculated from data obtained before the half-life period had been reached.

If, after the intravenous injection of a labelled substance, e.g. phospholipid or protein, the specific activity of the total substance in the blood is S_0 and after a

time, t , the specific activity is S_t , then it can be shown that $S_t = S_0 e^{-t/t_t}$ (4), where e is the base of natural logarithm and t_t the turnover time of the substance. By taking the natural logarithm on both sides of the equation we have $\log_e S_t = \log_e S_0 - \frac{1}{t_t} t$ (5). It follows from equation (5) that if the logarithm of the specific activity of the substance in the blood is plotted against time, a straight line is obtained provided our assumptions regarding the 'steady state' are correct. The slope of the straight line will be $\left(-\frac{1}{t_t}\right)$: i.e. the reciprocal of the turnover time (with a minus sign). Of course, if the amount of the substance in the circulating blood is known, the turnover rate can also be calculated.

This approach to turnover studies on blood constituents was made for the first time by Hahn and Hevesy (1939) in their investigations on plasma phospholipids. Zilversmit, Entenman, Fishler and Chaikoff (1943b), however, presented more extensive data on the same subject and have shown that the experimental observations permit the theoretical treatment just outlined.

The turnover of plasma proteins can be measured according to the same principles. All that is needed for this purpose is the preparation of a suitably labelled plasma protein. This can now be done quite satisfactorily *in vitro* with radioactive iodine. It has been shown that mildly iodinated plasma proteins behave as their normal fellows (McFarlane, 1956) and therefore such preparations can be used for turnover measurements.

CONCLUSION

The outline given in this article of the concept of dynamic equilibrium and of turnover measurements is of necessity sketchy, but the aim has been to stress principles rather than details. The use of isotopes in biological research is now so extensive that within the scope of a short article only some of those aspects of the subject could be treated that might be of use in the study of normal and disordered human metabolism.

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RADIOACTIVE ISOTOPES IN DIAGNOSIS

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THE use of radioactive isotopes in clinical investigation is still a relatively new procedure as there has been a freely available supply from nuclear reactors for less than ten years. During this period they have been used in many ways in the study of human disease. Some isotopes are now regularly employed in certain centres as diagnostic aids, whilst others are reserved for the investigation of special problems and unusual cases. However, with such new tools no clear-cut division between clinical research and diagnostic use is possible.

Certain general principles underlie the use of radioactive isotopes in the investigation of disease processes. The tissues of the body handle in the same way both the natural form and the radioactive isotope of an element. The latter, however, can be readily followed and measured by the characteristic radiations which it emits. The type of measuring device chosen depends upon the nature and energy of this radiation, but the radioactivity in any fluid sample can usually be measured easily and accurately. Furthermore, the concentration of a radioactive isotope can often be ascertained in a particular structure or region of the body if the radiation is sufficiently penetrating to reach an overlying counter.

A radioactive isotope may be administered in a simple inorganic form to trace an element naturally present, such as sodium or iodine. It may be built outside the body into a complex molecule and then administered in this form in order to follow the metabolism of the whole compound. For example, much can be learnt about the absorption of vitamin B₁₂ if a radioactive isotope of cobalt is used in its preparation. Some cells of the body take up and bind certain elements relatively firmly. In this way red blood cells can be labelled and their survival after transfusion can be followed. Many radioactive isotopes have been employed in clinical investigations and in a short survey these cannot all be recorded and discussed. Only a few of the more commonly used procedures will be considered as examples of the use to which these new tools may be put.

THYROID DISORDERS

The normal thyroid gland concentrates iodide from the plasma and utilizes it in the synthesis of thyroxine, which in due course is passed into the blood stream where it is bound to the plasma proteins. The true measure of thyroid activity is the rate at which its hormone is released into the circulation, but this is difficult to determine directly. The movement of

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iodide into the thyroid gland and its subsequent transfer into the blood in protein-bound form can be traced by the use of radioactive isotopes of iodine (Hamilton and Soley, 1939; Werner *et al.*, 1949; Goodwin *et al.*, 1951). The ones in common use are ^{131}I and ^{132}I . Both emit β - and γ -radiations and the latter can readily be detected by an external counter placed over the thyroid. In this way the fraction of the dose of the isotope present in the gland can be measured. The amount excreted in the urine can be determined provided that a complete collection is made. Radioactive iodine may be present in the blood either in the inorganic form before it has been taken up by the thyroid, or in an organic form after passage through the gland. The half-life of ^{131}I is eight days and it is more convenient to use and is easier to prepare. Measurements of its concentration in the thyroid and blood stream can be made for several days after its administration. It does, however, give a greater radiation dose to the gland than ^{132}I , which has a half-life of 2.4 hours, and when repeated tests are required or investigations are being made in young patients ^{132}I is the isotope of choice.

The use of radioactive iodine in the diagnosis of hyper- and hypothyroidism depends upon the assumption that the distribution of the tracer dose between the thyroid, blood, and urine reflects the activity of the gland in the synthesis and secretion of hormone. The interpretation of the tests is usually straightforward but may be difficult or impossible if the function of the gland has been altered either by previous iodine excess or deprivation or by antithyroid drugs, radiotherapy or surgery.

Tests of thyroid function with radioactive iodine rely on the measurement of either the rate of radioiodine transfer into the gland or of the amount that has arrived in the plasma after passage through the gland. Tests of the first type include simple measurements of uptake of radioiodine at intervals after administration of the dose, determination of the clearance of radioactive iodine in inorganic form from the blood by the thyroid, and measurements of the amount of radioactive iodine excreted in the urine, which forms an indirect assessment of the quantity that has been retained in the thyroid gland. The second type of test depends upon the determination of the amount of protein-bound radioactive iodine forty-eight or seventy-two hours after administration of the dose. A more reliable diagnosis can be made if two or more tests are used in combination, preferably one of the first type in association with a measurement of protein-bound radioactive iodine. The sensitivity of the different tests varies according to the nature of the thyroid disturbance and they have been extensively reviewed in recent years (Pochin, 1950; Myant, 1952; Foote *et al.*, 1952; Wayne, 1954; Fraser, 1956).

It is difficult to lay down standards for the diagnosis of thyrotoxicosis and myxædema on radioactive iodine tests. A wide variety of investigations is in use and each laboratory has to decide its range of normal values. These may vary from centre to centre, depending upon the type of equipment in use, the degree of accuracy attained and possibly on local conditions.

regarding the supply of iodide in food and water. In the diagnosis of thyrotoxicosis in Sheffield reliance is placed on the measurement of the radioactive iodine content of the thyroid gland and the protein-bound ^{131}I content of the serum.

In the majority of untreated thyrotoxic patients the uptake at four hours exceeds 40 per cent. of the dose and the protein-bound ^{131}I concentration in the serum at forty-eight hours is greater than 0.4 per cent. per litre (Wayne, 1954). The thyroid clearance rate in normal subjects at two hours after oral administration is usually between 10 and 60 ml./min. In thyrotoxic patients the rate is usually above 80 ml./min. and as a rule greatly exceeds this value.

The simplest test is the measurement of the neck-thigh ratio.

The more radioactive iodine that is taken up by the thyroid the less there is available for distribution elsewhere in the body. At two hours after an oral dose given to a fasting patient the radioactivity due to radioiodine is measured over the neck and thigh and the result is expressed as a ratio. Under the conditions described by Pochin (1950) the ratio seldom exceeded 7 in normal subjects and higher values were characteristically found in hyperthyroidism.

In diagnosing hyperthyroidism with radioactive iodine tests there are certain possible sources of error apart from technical inaccuracy. A high uptake of radioactive iodine occurs apart from thyrotoxicosis in a thyroid previously starved of iodine, as may be seen in endemic goitre or immediately after a period of treatment with antithyroid drugs. High levels of protein-bound radioactive iodine are still found after the successful treatment of thyrotoxicosis by surgery or radiation.

In hypothyroidism, the diagnosis is not so easily confirmed by tests with radioactive iodine. The uptake by the thyroid is depressed but in many mild cases there is a considerable overlap with the normal range. In this condition the urinary excretion of radioactive iodine is increased and the diagnosis may be confirmed by collecting the urine over different periods as described by Fraser *et al.* (1953). Although this is probably the most satisfactory radioactive iodine method for establishing the presence of hypothyroidism, it depends for its reliability upon accurate timing and completeness of urine collections and is inconvenient for the outpatient, who has to take away three large bottles.

In attempting to assess thyroid function with radioactive iodine it is unwise to attempt to draw a strict dividing line between the normal and abnormal, as there are all gradations of underactivity and overactivity. Nevertheless, in cases in which the diagnosis is in doubt on clinical grounds, great assistance can usually be obtained from radioactive iodine tracer studies. However, the decision as to whether therapy is required must be based on all the available criteria, both clinical and laboratory, and should never be made solely on the basis of radioactive iodine tests.

The radiation hazard to the thyroid gland must always be considered when these tests are contemplated. Obviously, if the diagnostic tests are preliminary to therapy with ^{131}I the tracer dose employed is negligible. If the test is to include a measurement of protein-bound radioactive iodine ^{131}I must be used and a dose of about $25\mu\text{c.}$ is usually required. This isotope

in such a dose should not be used in infants or children as in them the danger of producing malignant change in the thyroid with ionizing radiations is apparently greater than in adults (Simpson, Hempelmann and Fuller, 1955; Clark, 1955; Kilpatrick *et al.*, 1957). It should also be avoided in pregnancy and in lactating mothers as the ^{131}I is concentrated in the milk (Miller and Weetch, 1955). If radioactive iodine diagnostic tests are essential in cases of this type, ^{132}I should be used, but, with its short half-life, only an uptake and clearance rate can be satisfactorily measured.

The diagnostic use of radioactive iodine in carcinoma of the thyroid is considerably limited. Undifferentiated and most papillary tumours do not take up iodine and even in the more differentiated follicular carcinomas it is unusual to find much concentration of iodine. It is difficult to demonstrate radioactive iodine in a tumour if normal thyroid tissue is also present as the latter always possesses much greater ability to concentrate iodine. If, however, all the normal thyroid tissue has been removed by surgery or destroyed by radiation, a proportion of a tracer dose of radioactive iodine may occasionally be taken up by the primary tumour and the metastases. This may be demonstrated either in an autoradiograph made from a biopsy specimen or by external counting over an area where a metastasis is suspected. This affords confirmation of the nature of the tumour and evidence that it is suitable for treatment with radioactive iodine.

HÆMATOLOGICAL DISORDERS

Cobalt-labelled vitamin B₁₂.—Cobalt is an essential constituent of vitamin B₁₂ and in the biosynthesis this element can be supplied in a radioactive form as ^{56}Co or ^{58}Co which have half-lives of 80 and 70 days respectively (Booth and Mollin, 1956; Baker and Mollin, 1955; Bradley *et al.*, 1954). These isotopes are now used for clinical investigations in preference to ^{60}Co which has a half-life of 5.3 years, but was used in the earlier studies (Heinle *et al.*, 1952). In pernicious anæmia the absorption of vitamin B₁₂ is grossly impaired owing to the absence of the intrinsic factor secreted by the normal stomach. After a dose of vitamin B₁₂ labelled with radioactive cobalt is given by mouth to a patient with pernicious anæmia, 75 per cent. or more is recovered in the faeces, whereas in a healthy individual less than 40 per cent. is excreted in this way (Callender *et al.*, 1954). If at the same time as the oral administration of the labelled vitamin B₁₂ a parenteral injection of a large dose of 1 mg. of ordinary unlabelled vitamin B₁₂ is given, the radioactive material absorbed is in large measure flushed out in the urine (Schilling, 1953). In such circumstances in healthy individuals much of the radioactive dose absorbed from the intestine is recovered in the urine, whereas in patients with pernicious anæmia the urinary excretion is negligible. As it is much easier and pleasanter to work with urine rather than faeces the second type of test is more popular. It is, however, unnecessary and undesirable to use this test in the investigation of straightforward cases of pernicious anæmia which can be more satisfactorily

nosed by the examination of the peripheral blood, bone marrow and gastric juice. Tests of this type should be strictly reserved for the investigation and precise diagnosis of obscure types of megaloblastic anaemia.

Labelling of red blood cells with ^{32}P , ^{51}Cr and ^{86}Rb .—These isotopes of phosphorus, chromium and rubidium are taken up by red cells and retained in them with varying degrees of firmness (Reeve and Veall, 1949; Gray and Sterling, 1950; Mollison and Veall, 1955; Tudhope and Wilson, 1956). The red cells labelled in this way can be reinjected into the circulation. The extent of the dilution of the radioactive cells affords a measurement of the total red cell volume:—

$$\text{Red cell volume} = \frac{\text{Radioactivity injected in labelled cells}}{\text{Radioactivity per unit volume of red cells in the circulation}}$$

Sufficient ^{51}Cr is taken up within half an hour by a suspension of red cells at room temperature and a measurement of red cell volume can be completed within two hours of withdrawing the initial blood for labelling.

Investigation of red cell volume is still essentially a research procedure but it is clear that the use of ^{51}Cr affords a rapid method of measurement which may prove to be of considerable practical use in the assessment of the extent of hæmorrhage. A further advantage is that the ^{51}Cr is securely retained in the labelled cells and after their destruction is not taken up by new cells. The survival of the cells can thus be followed in the blood for several weeks (Ebaugh *et al.*, 1953; Read *et al.*, 1954). One practical use of this observation is in testing the compatibility of blood for transfusions in difficult cases (Mollison and Cutbush, 1955). A very small fraction of the cells to be transfused is labelled with ^{51}Cr and injected into the recipient. Their survival can be followed by serial measurements of the radioactivity of the blood. If the cells are incompatible the radioactivity drops sharply as they are rapidly removed from the circulation.

Absorption and utilization of ^{59}Fe .—A radioactive isotope can be used to measure the extent of absorption of iron given by mouth. The utilization of radioactive iron after either absorption from the alimentary canal or parenteral injection can be studied by measuring the amount of radioactivity that appears in newly formed red cells. Many interesting investigations into the mechanism of the development of anaemia have been made in this way but these techniques still remain essentially in the field of research rather than of clinical diagnosis.

THE CIRCULATION

Radioactive isotopes have been used in many ways to study the circulation. The velocity of blood flow has been measured in the veins of the lower limb by injecting radioactive sodium into a vein on the dorsum of the foot and timing its arrival under a counter placed over the groin. Slowing of the rate of venous blood flow may be an important factor in the development of venous thromboses (Wright, 1952). Attempts have also been made to measure the efficiency of local circulation by injecting a small quantity

of ^{24}Na in isotonic solution into a deep structure such as muscle. The removal of the ^{24}Na can be determined by placing a suitable external counter over the depot. One factor in determining the rate of disappearance of the radioactive sodium from the injection site is the blood flow in the surrounding capillaries (Kety, 1949), although there are probably other factors of importance not directly related to the circulation (Miller and Wilson, 1951; McGirr, 1952). Practical use has been made of this technique in determining the viability of skin flaps in grafting operations. If the proximal end of the graft is clamped a normal rate of removal of injected radioactive sodium indicates that a satisfactory circulation has been established through the distal end (Barron and Veall, 1952).

WATER AND ELECTROLYTE METABOLISM

In the investigation of water and electrolyte abnormalities, the only methods of study until recently were the measurement of the concentration of electrolytes in body fluids, particularly the plasma, and the performance of a metabolic balance study. The latter, which may involve the measurement of the intake and output of potassium, sodium and chloride, is capable of demonstrating a gain or loss in the body content of these elements over the period of study. By these methods alone, however, the total amount in the body cannot be determined. This can now be done by the use of radioactive isotopes. For example, if ^{24}Na , a radioactive isotope of sodium, is injected intravenously it rapidly mixes with the stable ^{23}Na in the body. The extent of the dilution of the radioactive sodium in the body pool is measured and the total mass of sodium in the body available for exchange with the isotope can be calculated (Miller and Wilson, 1953). Using techniques of this type, the total 'exchangeable' amounts of potassium, chloride and water present in the living patient can be determined. These investigations are still confined for the most part to the elucidation of research problems but they are adding considerably to our knowledge of the distribution of water and electrolytes in both health and disease (Moore *et al.*, 1954).

LOCALIZATION OF CEREBRAL TUMOURS

It is often difficult to be certain of the presence and position of a cerebral tumour, even after the most detailed clinical and radiological examination. One advance in this problem has been made by using radioactive isotopes. A substance which is concentrated in actively growing tissue is injected in a labelled form so that its distribution within the brain can readily be followed. Cerebral tumour tissue takes up more than the surrounding normal brain. As might be anticipated in these circumstances, vascular tumours such as meningiomas, glioblastomas and metastatic carcinomas are more readily diagnosed than the better differentiated and more slowly growing astrocytomas.

Two techniques have been used. The first depends upon the internal exploration of the skull with a small counting device (Silverstone

1949; Morley and Jefferson, 1952). Radioactive phosphate in the form of ^{32}P is given before operation and then a miniature Geiger counter designed in the form of a probe is passed through a burr hole into the brain. Phosphate is concentrated in rapidly growing tumours and a region of increased radioactivity may represent the site of a neoplasm. In this way the neurosurgeon is guided to the lesion and a biopsy can be taken from the appropriate region with minimal disturbance of normal tissue.

The second method uses the same principle of concentration in rapidly dividing cells but uses an external counting system. Localization depends upon counting at many points over the skull. In these conditions a radioactive isotope must be used which emits gamma radiation, and ^{32}P , a pure β -emitter, is not suitable. ^{131}I has been most extensively employed either in the form of diiodofluorescein or iodinated human serum albumin (Peyton *et al.*, 1952; Dunbar and Ray, 1954; Seaman *et al.*, 1954). These external counting techniques may be helpful when the neoplasm lies in a cerebral hemisphere. When it is situated in the posterior fossa, at the base of the brain, or in the pituitary region, the method is at present of doubtful value.

RADIATION EXPOSURE AND HEALTH HAZARDS IN DIAGNOSTIC TESTS

Increasing attention is now being paid to the possible dangers to health of ionizing radiations, and there is evidence that they may be a factor in leading to the development of malignant disease (Medical Research Council, 1956). In man the investigations have chiefly concerned the long-term results of external x-irradiation in relation to the subsequent development of leukæmia and carcinoma of the thyroid. It is possible that infants may be more susceptible in this way than adults. There is every reason to suppose that internal irradiation of tissues from administered artificial radioactive isotopes carries the same dangers as an equivalent exposure to ionizing irradiation from an external source. Information about the precise hazards is still meagre and it is important to preserve a sense of proportion. The incidence of malignant change after exposure to irradiation is extremely low and the diagnostic aid that can be obtained from properly applied tracer tests with some radioactive isotopes may be great. Like many powerful modern pharmacological agents, ionizing radiations can be both beneficial and harmful and knowledge and judgment are required in their application.

The danger of malignant disease following irradiation apparently increases in proportion to the dose. In all diagnostic tests involving radioactive materials, the exposure should be kept as small as possible. Advances in the design of counting equipment permit accurate measurements to be made with smaller doses of radioactive isotopes. Short half-life isotopes should be used whenever possible, for example ^{24}Na (half-life 15 hours) in preference to ^{22}Na (half-life 2.3 years). Particular care must be exercised if the isotope is liable to be concentrated in a certain tissue and retained in the body. For instance, much sodium is incorporated and firmly fixed in growing bone,

and for this reason the long half-life sodium isotope should not be used in children. In other cases it may be possible to flush out from the body much of the radioactive material at the end of the test by giving a large dose of the corresponding non-radioactive material, as in the vitamin B₁₂ tests with labelled cobalt. In these and many other ways the radiation dose can be substantially reduced and this should always be the constant aim of the doctor and physicist in the use of all diagnostic procedures involving exposure to ionizing radiations.

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RADIOACTIVE ISOTOPES IN THERAPY

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IN 1948, artificially produced radioactive isotopes first became available for use in medicine in Great Britain. The early optimistic and ill-founded hopes of obtaining a high rate of dramatic cures in malignant disease by means of these isotopes has not been realized. Nevertheless, some of the artificially produced radioactive isotopes have contributed real and fundamental advances in the treatment of many types of malignant disease, and in certain sites (e.g. polycythæmia vera) these isotopes offer the best form of treatment.

The ideal method of treating malignant disease would obviously be by means of a non-toxic chemotherapeutic agent acting specifically, in a lethal manner, on neoplastic cells. In spite of great ingenuity, effort and expense, no such 'aqua vitæ' has yet been discovered. Another approach to this vital problem would be the discovery of any substance possessing the characteristic of being specifically and permanently concentrated to a high degree by neoplastic cells. By artificial means such a substance could be produced in radioactive form and the malignant cells specifically concentrating such a radioactive substance would bring about their own destruction. At present the only such substance in clinical use is radioactive iodine (^{131}I and ^{132}I).

In the treatment of malignant disease artificially produced radioactive isotopes are used in many and varied forms. The selection of any particular isotope technique is in large measure dictated by the exact requirements of the case under consideration. The wide variety of techniques available for the treatment of certain malignant processes by means of radioactive isotopes affords a most flexible, adaptable, essential tool to the armamentarium of the radiotherapist. The clinical applications of the therapeutic uses of isotopes are comparatively new, with the result that modifications and improvement in techniques are constantly taking place.

ARTIFICIALLY PRODUCED RADIOACTIVE ISOTOPES USED FOR EXTERNAL IRRADIATION

The great advantages of high energy irradiation in the 1 to 4 million volt range (i.e. supervoltage therapy), over conventional x-ray therapy machines of around 250 kV, have become fully appreciated in recent years. With such high energy beams skin reactions are minimal, systemic upset very much less, penetration is greater and higher tumour doses can be delivered with greater accuracy. Certain artificially produced isotopes (Cobalt-60, Cesium-137) emit radiations of high energy and are now obtainable in high

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activities of around 1000 to 2000 curies. These isotopes are used as sources of high energy radiation and because of their high activity they can be used at treating distances of 50 to 100 cm., thus giving the equivalent of super-voltage x-ray machines (fig. 1). The

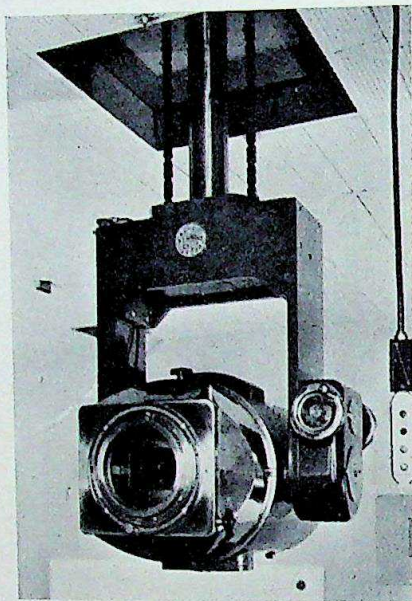


FIG. 1.—The telecaesium (^{137}Cs) unit recently installed in the Downs branch of the Royal Marsden Hospital. This is the first apparatus of its kind in clinical use in this country.

'radium bomb' (fig. 2), containing 5 to 10 grammes of radium element, has been in use in a number of radiotherapy units for many years. Such low activity sources require short treating distances (i.e. skin-source distance) of 5 to 8 cm.—because of the inverse square law the intensity of radiation falls off rapidly. This type of apparatus is only suitable for the treatment of superficially placed malignant lesions, e.g. larynx and pharynx. Artificially produced radioactive cobalt (^{60}Co) may be used as the radiation source in place of radium element.

RADIOACTIVE ISOTOPES USED FOR IMPLANTATION

(i.e. INTERSTITIAL TECHNIQUES)

In certain sites (e.g. tongue and urinary bladder) circumscribed malignant lesions can often be treated most

effectively by local implants of radioactive substances directly into the growth and the immediately adjacent tissues. Such methods permit the irradiation to be confined to a small volume of tissue which can be treated to a relatively high dose level over a period of approximately seven days. If this technique is used it is essential that the radioactive sources should be implanted with absolute accuracy and precision. Until recent years only radium needles or radon seeds were available for this method of treatment and, because of mechanical and technical difficulties, it was often impossible to

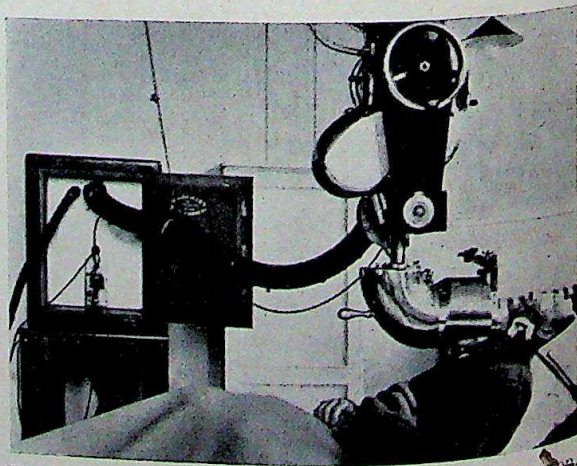


FIG. 2.—The radium-bomb irradiating sub-mental region. Note the safe to which the radium is transferred pneumatically when not in use.

obtain accurate disposition of the radioactive sources. Many of the technical difficulties pertaining to interstitial techniques have been overcome by using artificially produced radioactive isotopes.

Radioactive tantalum wire (^{182}Ta), coated with a thin (0.1 mm.) layer of platinum to absorb the beta-rays, can be implanted with a high degree of accuracy, by means of a special introducer (fig. 3), into the muscle wall of the bladder in certain cases of cancer of the urinary bladder (fig. 4, 5). As these wires are flexible, they accommodate themselves to the varying contours of the bladder wall, and when the period of irradiation has been completed they can easily be removed per urethram. In the treatment of certain bladder neoplasms this technique offers many advantages over the older methods employing radium needles and radon seeds. Because of its flexibility tantalum wire proves a most suitable substance for the preparation of external applicators (moulds) used in the treatment of skin cancers, especially when convex or concave surfaces are involved.

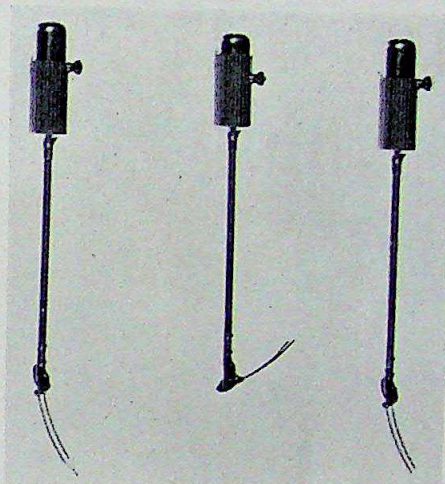


FIG. 3.—Radioactive tantalum wire introducer.

Radioactive cobalt needles are now often used as a substitute for radium needles. Small cobalt beads may be loaded inside thin nylon tubes which are used to implant malignant growths in certain sites; these flexible sources can readily be withdrawn from the tissues without having to perform a second 'operation of exposure'. The implantation of platinum-coated gold grains by means of a special gun (Royal Marsden Hospital pattern, fig. 6) offers a most convenient method of applying interstitial irradiation (fig. 7). Magazines, each containing 15 grains, are irradiated in the atomic pile; they can be obtained at short notice and if not used can be re-irradiated. The gun, when primed, will deliver 15 grains (i.e. the contents of one magazine) at one loading. For routine use these grains offer many advantages over radon seeds.

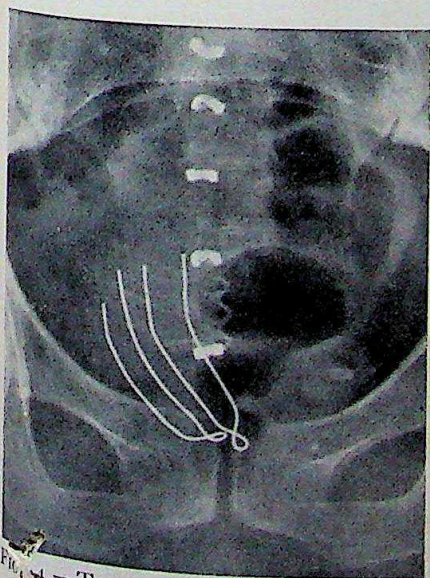


FIG. 4.—Two radioactive tantalum 'wires' in position in bladder tumour.

In recent years the importance of

'hormone-dependence' in tumour growth (e.g. breast and prostate) has become fully appreciated. On this basis various methods are used to alter the hormone balance of the patient in the hope of inducing tumour regression. Cases of advanced carcinoma of the breast, which have failed to respond to all forms of routine treatment, may at times

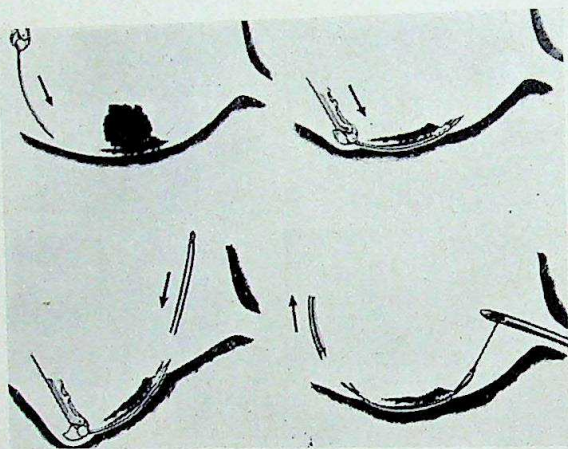


FIG. 5.—Implantation of bladder tumour, using radioactive tantalum wire.

derive some benefit from pituitary ablation. This measure can be accomplished by implanting a radioactive source into the pituitary gland (fig. 8) by means of a long needle introduced transnasally through the sphenoidal air sinus and the floor of the pituitary fossa. Pellets of radioactive yttrium oxide (^{90}Y) are most suitable for this technique as this isotope emits only beta-rays. These rays are highly destructive, but act over a very short distance, thus producing a small zone of necrosis and thereby a local 'radiation hypophysectomy'. High-activity radon seeds were used in some centres, but the additional gamma-rays from this source possess much greater powers of penetration and some patients so treated developed delayed radiation-induced optic nerve damage. Only a small proportion of patients treated by this technique derive any appreciable benefit.

Beta-ray applicators.—Beta-rays penetrate the tissues for only very short distances (1 to 2 millimetres) and this characteristic is utilized in the treatment of certain superficial lesions. Beta-ray therapy is

often used in the treatment of pathological processes involving the eye (e.g. Mooren's ulcer, superficial punctate keratitis, rosacea keratitis, vascularization of the cornea and allergic conjunctivitis). This type of radiation is most conveniently given by means of a plastic eye-shell (fig. 9), which is coated with radioactive strontium (^{90}Sr). Radioactive phosphorus (^{32}P) can be incorporated in polythene sheets and used in the treatment of certain skin conditions.

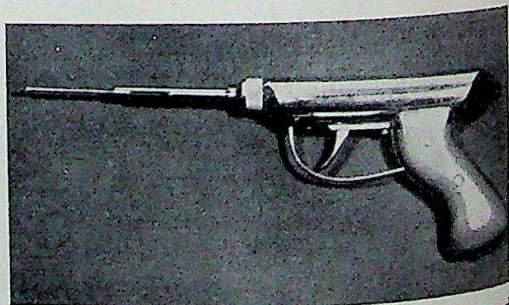


FIG. 6.—Royal Marsden Hospital pattern gun used for the implantation of radioactive gold grains.

RADIOACTIVE ISOTOPES USED LOCALLY IN LIQUID FORM

Malignant disease arising primarily in various sites (especially breast, lung and ovary) often involves the pleural or peritoneal membrane, causing the formation of massive effusions of fluid.

These effusions give rise to marked symptoms and require frequent aspirations. If left untreated the patient is soon reduced to a sorry state of misery.

The instillation of radioactive colloidal gold (fig. 10) into the involved serous cavity, following the aspiration of as much fluid as possible, gives rise to appreciable benefit in 30 per cent. to 50 per cent. of patients so treated. A colloid is used in order to prevent the absorption of gold into the blood stream. After the injection of the colloidal gold the patient is tipped into various positions in order to bring all parts of the involved serous cavity into intimate contact with the colloid. Radioactive gold in colloid form emits mainly beta-rays, as well as a small proportion of gamma-radiation. The gold particles are fairly rapidly deposited on the serous membrane where the radiation gives rise to some degree of fibrosis, which is probably mainly responsible for the inhibition of fluid formation. The full



FIG. 7.—Radioactive gold grain implant of secondary malignant gland.

benefit from this form of treatment may take some weeks to manifest itself. Following the intracavitary insertion of radioactive colloidal gold, effusions often re-form quite rapidly. If this postoperative fluid gives rise to appreciable symptoms it can safely be aspirated any time after the fifth day—by then nearly all the radioactivity has been taken up by the serous membrane and any fluid that is aspirated possesses little or no activity.

Malignant disease of the urinary bladder may, in a small proportion of cases, first present in the form of multiple small superficial tumours, diffusely spread over all areas of the bladder (fig. 11) with intervening areas

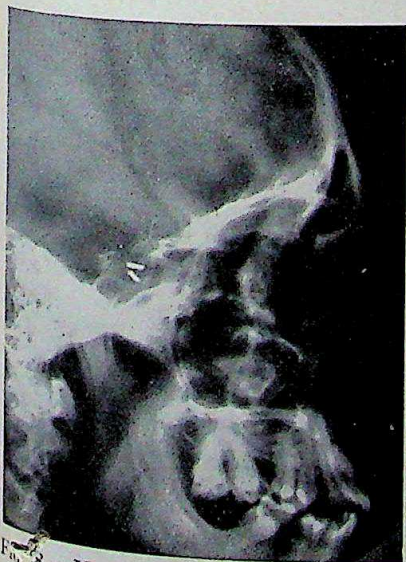


FIG. 8.—X-ray of skull, showing yttrium colloid implant of pituitary gland.

of mossy abnormal pre-malignant mucosa. The proper management of this type of lesion requires treatment to be directed to the whole of the bladder mucosa. This aim can be accomplished by using some form of intravesical irradiation. Such techniques can be administered by introducing radioactive colloidal gold via a catheter or by inserting into the cavity of the bladder a special type of balloon catheter (fig. 12) which is filled with radioactive bromine. By virtue of the proximity of the radiation sources to the bladder wall these techniques give a rapid 'fall-off' in the intensity of irradiation; it is therefore possible to administer a high dose of irradiation to the surface mucosa and at the same time spare the underlying tissues of the bladder wall from excessive damage.

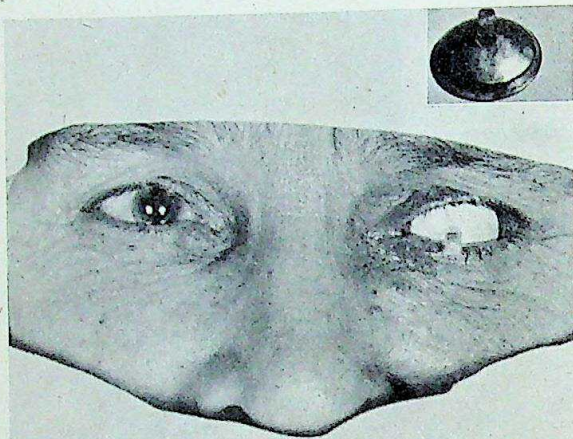


FIG. 9.—Beta-ray applicator: strontium (^{90}Sr) eye-shell.

RADIOACTIVE ISOTOPES IN LIQUID FORM USED SYSTEMICALLY

In this category the isotopes in common use are iodine (^{131}I) and phosphorus (^{32}P). The body cells deal with these artificial radioactive isotopes in exactly the same manner as their naturally occurring non-active counterparts.

Radioactive iodine (^{131}I) in the treatment of thyrotoxicosis.— ^{131}I , administered orally, offers a most satisfactory method of treating thyrotoxicosis, and the only factor which prevents this form of treatment from being universally accepted as the method of choice is the hypothetical risk of inducing malignant change in the thyroid gland. Many thousands of patients have now been treated by ^{131}I in various centres all over the world and to date no case of thyroid cancer has been reported. If there is any real risk at all it must be extremely small and after another few years elapse it is almost certain that ^{131}I will become generally accepted

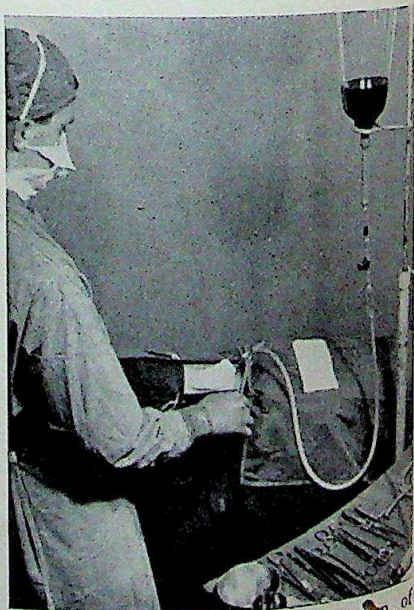


FIG. 10.—Intra-peritoneal insertion of radioactive colloidal gold for treatment of malignant peritoneal effusion.

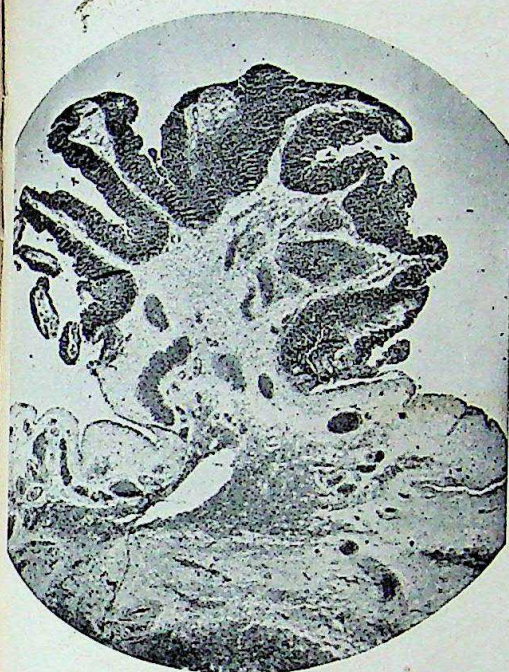


FIG. 11.—Small superficial papillary tumour (x 25). When the whole bladder mucosa is involved by such lesions intracavitary irradiation offers a suitable method of treatment.

LATEX BAG FOR INTRACAVITARY IRRADIATION OF THE BLADDER

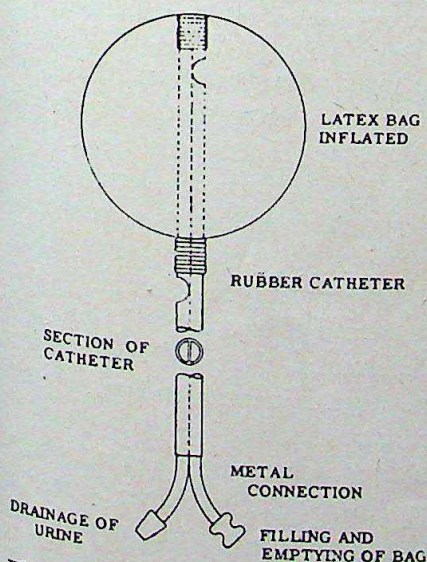


FIG. 12.—Balloon catheter for intracavitary irradiation, using radioactive bromine.

as the best method of treating thyrotoxicosis. At present a very conservative approach is generally recommended and ^{131}I is reserved for specially selected patients: e.g. those over the age of 45 years, those with recurrence of toxic symptoms following partial thyroidectomy (here the results of a second operation are poor and the risk of damage to the recurrent laryngeal nerves higher), and those in poor general condition, as in cases of advanced cardiac failure.

The radioactive iodine is given orally. On entering the blood stream the iodine is taken up by the thyroid gland in a highly selective manner, where it is used to form thyroxine. While concentrated in the gland, highly specific and localized irradiation of the thyroid takes place; this irradiation reduces the activity of the constituent cells and thus brings about a cure of the disease. Various schemes are used for estimating the dose required for any particular patient and the treatment may be given by means of a single dose or repeated smaller fractions. Some improvement in symptoms is often observed after four weeks, but the full benefit of treatment is not evident until three months have elapsed. If no benefit is observed from a single dose at the end of two months, it is unlikely that any further improvement will take place and the dose should be repeated.

Smooth hyperplastic toxic glands respond to much lower dosages than do nodular glands. Patients with severe toxic symptoms should first be brought under control by bed rest, sedation and antithyroid drugs, because in rare cases ^{131}I can precipitate a thyrotoxic crisis.

Following treatment by means of ^{131}I a small proportion (approximately 10 per cent.) of patients will become hypothyroid; in the majority of these patients this state is only of short duration (i.e. 'temporary post- ^{131}I hypothyroidism'). The initiation of permanent myxœdema is at times purposely induced by ^{131}I in patients with severe anginal pain due to advanced cardiac disease; this brings about a general lowering of metabolic rate.

Iodine-131 in the treatment of carcinoma of the thyroid gland.—The initial hope that this isotope, by virtue of its highly selective uptake by the thyroid gland, would provide the answer to the treatment of thyroid cancer has not been realized. Generally speaking, only the more differentiated types of growth show worthwhile uptake of ^{131}I , and then always to a much smaller degree than normally functioning thyroid tissue. Hence it follows that in order to obtain maximum uptake of ^{131}I in malignant thyroid

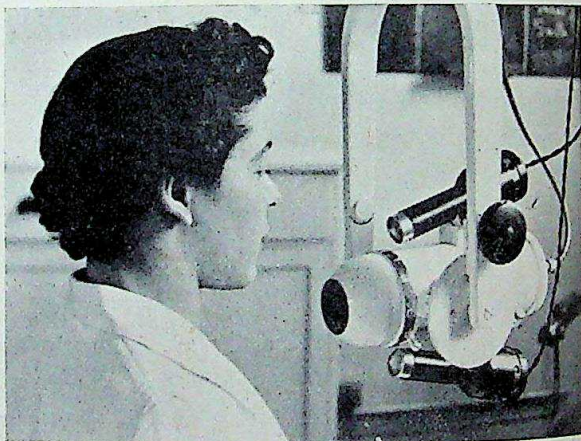


FIG. 13.—Estimation of radioactive iodine (^{131}I) uptake by thyroid gland by means of scintillation counter.

tissue as much normal thyroid as possible should be removed, and this may be accomplished by either surgical excision (the more rapid method) or administering a large dose of ^{131}I (ablation dose). About eight to ten weeks later a small tracer (1 mc.) dose of ^{131}I is given and its uptake is determined by external counting (fig. 13, 14). This is followed by a therapeutic dose (100 to 150 mc.) and this procedure is repeated at two- to six-monthly intervals. The uptake of iodine in malignant thyroid tissue may be increased by the administration of antithyroid drugs for a period of two weeks before giving a therapeutic dose; conversely, the administration of any iodine-containing medicine should never be given to such patients as it completely prevents the thyroid tissue from taking up iodine for many months.

Radioactive phosphorus (^{32}P).—Treatment of polycythæmia vera by means of this isotope is now accepted as the method of choice. Patients with this disease have an increased blood volume and red cell mass and blood viscosity. Their numerous and distressing symptoms are due to these hæmodynamic abnormalities, which can be verified by blood volume studies using

red blood cells 'labelled' with radioactive chromium (^{51}Cr). These patients are best treated by 'dextran' replacement transfusion and simultaneous venesection, followed by the intravenous injection of radioactive phosphorus (approximately 5 to 7 mc.). The whole treatment can be completed in two

to three days. Subsequent injections of ^{32}P are given as required. In this condition the hæmopoietic bone marrow is hyperplastic; it therefore readily takes up ^{32}P and the radiation thereby received reduces its activity.

Lymphosarcoma in its diffuse and generalized form, presenting as massive enlargement of many lymph glands, can be adequately treated by intravenous ^{32}P , which causes a dramatic reduction in the size of the nodes. Radioactive phosphorus is also often used in the treatment of chronic lymphatic and myelo-

^{131}I IN CARCINOMA OF THYROID
WHOLE BODY SCAN WITH EKCO SCINTILLATION
COUNTER AFTER ADMINISTRATION OF 500 μC ^{131}I
(PRIMARY TUMOUR PREVIOUSLY TREATED BY
SURGERY & ^{131}I)

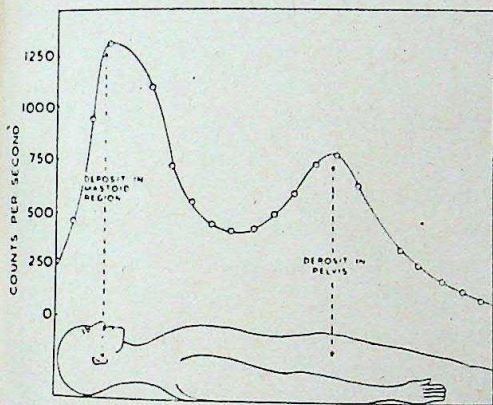


Fig. 14.—Carcinoma of thyroid: Detection of metastatic deposits by profile scan, using a scintillation counter.

genous leukaemia, by means of repeated small doses.

CONCLUSION

From this review it is obvious that artificial radioactive isotopes are an essential tool in the management of a large number of malignant processes. This therapeutic weapon is comparatively new and it is certain that it will be directed at many fresh targets in the near future.

I wish to express my gratitude to Professor D. W. Smithers, Director of the Radiotherapy Department, Royal Marsden Hospital, who initiated many of the techniques referred to in this article, to the staff of the isotope and photographic departments, and to Miss Johnson, for their cooperation.

A HOSPITAL RADIOACTIVE ISOTOPE UNIT

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WITH the expanding role of radioactive isotopes in diagnosis, treatment and research in modern medicine, it is apparent that facilities for their use will need to be available in an increasing number of hospitals, particularly in the investigation and treatment of thyroid disorders. At the present time these facilities are mainly restricted to teaching hospitals, and to a few of the larger non-teaching hospitals, but they will soon become a necessity in many more centres and they should certainly be available in towns with a population greater than 200,000, or less if situated some distance from a large centre. Relatively simple equipment is now available, supplies are easily obtained from the Atomic Energy Research Establishment, Harwell, and the Radiochemical Centre, Amersham, and the capital cost is not great in comparison, for example, with a diagnostic x-ray or radiotherapy department.

Radioactive isotopes may be needed in research by various departments of the hospital, but unless some special long-term project is involved it is better if the facilities are centralized in one laboratory. In this way the expert advice of a physicist is available for the constant supervision of techniques and equipment and the technicians can be thoroughly trained in the particular discipline of this type of work. It saves duplication of equipment and leads to more accurate results as many errors are unwittingly made by those unaccustomed to handling and measuring radioactive material.

SITUATION

The location of the laboratory within a hospital will no doubt depend upon the space that is available: it could be in an established general or chemical pathology laboratory, or it could be in, or adjacent to, a radiotherapy department. The latter is advisable as responsibility for treatment with radioactive isotopes rests with the radiotherapist and, as the assistance of a physicist is essential, use can often be made of the physics service already existing in most modern radiotherapy departments. Also there may be space already present for storing radium or radon seeds that could be expanded as a store-room for other radioactive isotopes.

One or more rooms are necessary for examining patients and measuring material; in addition, a separate room is needed to keep the isotopes, for preparing them in suitable form for administration and also for storing heavily contaminated excretions, particularly urine, before they can be

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disposed of. There is, however, one serious objection to the siting of an isotope laboratory in a radiotherapy department, and that is the question of radioactive background, for the natural 'cosmic' background can be affected many fold by stray radiations from installations such as high-voltage x-ray or radiocobalt teletherapy units, if these be too near the counting equipment. Similarly the store-room must not be too near the 'counting house' or, if it is, it must be heavily screened.

PRECAUTIONS FOR PERSONNEL AND PATIENTS

It is unnecessary for technicians to wear special clothing when handling the small amounts of radioactive material used in tracer investigations for diagnosis or research and occasional therapeutic doses, as there is little danger from the effects of whole body radiation. It is a sensible precaution, however, for everyone to wear some form of film badge to check external exposure. The main danger is from direct contact of material on the hands and its subsequent possible ingestion. Consequently no smoking or eating is allowed while preparing samples. Rubber gloves should be worn when handling active material ($>10 \mu\text{C.}$) and at all times great care must be taken that no material is spilt on the hands. Some form of monitor should be available to check the possibility of contamination of hands if there has been any question of a spill and if significant radioactivity is detected they must be thoroughly washed and scrubbed.

Preparation of active material should be done behind lead screens; simple remote handling devices and piston-operated pipettes and the like should be available and used for all preparations above the microcurie level. For further details on this subject, the article by Fay (1952) should be consulted.

For patients receiving tracer doses for investigation no special precaution is necessary for themselves or the nursing staff. Urine is the most likely excretion to be radioactive and in most investigations this is collected for measurement. Patients undergoing treatment with radioactive iodine or phosphorus pass highly active urine for three or four days. They can be treated in an ordinary hospital ward, but should have their own marked crockery, and a bedpan should be kept for their sole use. Nurses should wear rubber gloves and aprons when handling the bedpans or contaminated sheets but, unless a large number of cases is being treated, no other special precautions are necessary. Patients should not be treated if there is a possibility that they may vomit the dose or if they be incontinent of urine. The urine can be kept in Winchester bottles on a balcony or similar site away from patients, from where it is collected by the staff of the laboratory every day and stored until it has decayed sufficiently to be disposed of down the sluice. Under present regulations the maximum amount that can be flushed down the normal sewage disposal system is 100 microcuries per week or 1 millicurie per week. After an average therapeutic dose for thyrotoxicosis such urine has to be kept for two or three weeks; after an ablative

dose to destroy the gland it may have to be kept for as long as two months.

For the general run of patient treated no other precautions need be taken in the ward, either for the patients, their visitors or the nursing staff. By having patients in several wards it is most unlikely that any particular nurse will receive any significant radiation. If, however, many patients are treated in a special ward consideration must be given to whole body radiation that could be received by the nursing staff from frequent contact with many patients. They should wear a film badge and should be trained in the necessary discipline such as that advised for the laboratory technicians.

Should the patient be incontinent of urine or inadvertently spill urine, sheets and other contaminated bedding or clothing must be removed and kept apart until free from radioactivity. It is inadvisable to give therapeutic doses to any patient who is incontinent of urine or who has diarrhoea. Constant consideration has to be given to these precautions, for care is apt to lapse with familiarity and the whole subject should be reviewed once or twice a year.

EQUIPMENT

Laboratory benches or tables on which radioactive material is handled, either before administration to the patient or during preparation for counting, should be covered with some form of easily removable non-absorbable material such as polythene. This is easily changed if there is an accidental spill and it saves contamination of permanent woodwork. A simple Geiger-Müller monitor is required to check possible contamination of hands, clothing, benches and syringes, beakers, pipettes and the like used in the preparation of samples.

GEIGER-MÜLLER COUNTERS

Geiger-Müller counters have heretofore been the most widely used type of instrument for measuring radioactivity in medical work. Briefly, they consist of a gas-filled cylindrical vessel fitted with a pair of electrodes across which an electrical potential is applied. When the gas is ionized by radioactive material equal numbers of positively and negatively charged ions are formed which are attracted towards the oppositely charged electrode, resulting in a current through the circuit which can be measured and recorded electronically.

They are constructed in several forms: an 'end-window' type for measuring small quantities of dry material; 'liquid counters' for measuring fluids. They can be arranged in rings for detecting activity in large quantities of urine or stool or for estimating the uptake in the thyroid gland and indeed in many other forms for special needs. Fig. 1 illustrates three counters arranged in a triangle and fixed to a chair for the measurement of radioactivity in the thyroid gland following the administration of radioiodine (Langmead and Birchall, 1957).

Geiger-Müller counters are essential for measuring purely β -particle-emitting isotopes and they have the advantage that the background count

Fig. 1.—
a tri-
thyroid

thyroid
a nodu-
carcino-
illustrat-
scanning
detectin-
marrow
Wether-
The
Particul-
cylindri-

is very low. The chief disadvantages, compared with a scintillation counter, are: their poor efficiency for detecting γ -rays; the necessity to wash a liquid counter at least ten times between each specimen to be measured and the great care that has to be taken in the preparation of dried samples to see that the geometry of similar samples to be counted is the same.

SCINTILLATION COUNTERS

Scintillation counters are becoming more popular, as they are 10 to 20 times as efficient as a Geiger-Müller counter in the detection of γ -rays. A wide

range of substances, called phosphors, have the property of emitting light from secondary electrons released by the impact of γ -rays. These minute scintillations are magnified in a photomultiplier tube and the resulting electrical pulses are then counted with electronic equipment. They are of no use for detecting β -particles and the other main disadvantage is the relatively high background count due to their high sensitivity for γ -rays.

Two main types are in common use. A directional counter, which can be used for detecting γ -rays from a distance, which is of particular value for surface counting over the body; it can be used for measuring



FIG. 1.—Three Geiger-Müller counters arranged in a triangle and fixed to a chair for measuring thyroid uptake.

thyroid uptake, and for scanning the neck to determine, for instance, whether a nodule in the thyroid is 'hot' or 'cold'; or for determining whether a carcinoma of the thyroid will take up radioactive iodine. Such a role is illustrated in fig. 2, the counter in this instance being fixed to an automatic scanning device (Langmead and Birchall, 1957). They are also used for detecting activity in other organs, e.g. the heart, liver, spleen and bone marrow after administration of radioactive iron (Ledlie and Baxter, 1954; Wetherley-Mein *et al.*, 1956).

The other form commonly used is the 'well-type' counter which is particularly useful for measuring small samples of body fluids. Small glass cylindrical tubes (6 cm. high, 1.5 cm. in diameter, and 10 ml. capacity)

can be previously prepared with the samples which can then be counted successively by inserting the tubes into the 'well' without the necessity of repeated washings between each sample (*cf.* Geiger-Müller liquid counters). Very small amounts of radioactivity can be recorded by this means, though it must be re-emphasized that the background count is much higher than that of a Geiger-Müller counter and this may be a serious disadvantage.

It can be seen that there is now a wide variety of radiation detectors available according to particular needs. With the sort of counters mentioned many different types of investigation can be undertaken with most of the more frequently used radioactive isotopes, a notable exception being tritium for which special counting equipment is necessary. For further information on this subject the reader is referred to the article by Veall (1952).

ELECTRONIC

RECORDING EQUIPMENT

Some form of electronic recording equipment is necessary to register the impulses received by the counters. These are of two main types, the scaler and ratemeter. A scaler records electronically the number of impulses received by a counter and registers them automatically. It can be relatively simple or extremely complex. Some of the more elaborate ones have a time signal incorporated, and can be set to record the number of impulses received in a prearranged time; alternatively they can be set to record the time taken for a prearranged number of impulses. The more simple ones have to be used with a stop-watch but, unless a great deal of counting has to be done, this is no great hardship and, as they have the merit of being simple, there is less to go wrong.

A ratemeter is used for samples containing more radioactivity, e.g. a 24-hour sample of urine after radioiodine. A dial is incorporated in the equipment and calibrated to record directly the number of impulses being received each second. This saves a lot of time, but it is of no value for counting low-activity samples. It is essential if some form of automatic

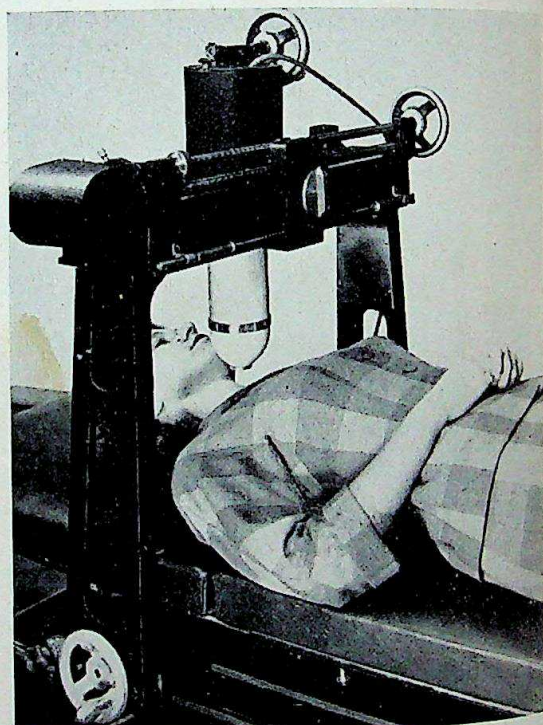


FIG. 2.—A directional scintillation counter incorporated in an automatic scanning device for mapping radioactivity in the thyroid.

pen recording is needed such as may be used in the determination of cardiac output from external counting over the heart.

Various other forms of equipment, e.g. dose meter, pulse analyser and pulse generator, may be needed in larger laboratories, but these fall outside the scope of the present article.

ROLE OF A GENERAL RADIOACTIVE ISOTOPE LABORATORY

This can be illustrated by the work performed in the laboratory at St. Thomas's Hospital which is staffed by a physician, a physicist and two technicians, one of whom is primarily trained in chemical pathology. The main routine work performed concerns the investigation of thyroid disorders with radioiodine of which an average of 10 cases are seen weekly. Other investigations, both for diagnosis and research, have included the use of isotopes of sodium, potassium, bromine, and chromium; vitamin B₁₂ labelled by biosynthesis with radioactive cobalt; and human serum albumin labelled with radioiodine. The latter has been used for estimation of plasma volume, for measurement of cardiac output, and for the study of albumin degradation in obscure forms of hypoproteinaemia. In 1956, 97 separate investigations were performed with these isotopes.

In collaboration with the radiotherapy department treatment is undertaken with radioactive iodine, phosphorus and colloidal gold. In 1956, 36 cases of thyrotoxicosis were treated; the thyroid has been ablated to induce myxoedema in six cases of chronic congestive failure, and eight cases of carcinoma of the thyroid have been investigated with a view to treatment. There were four cases of polycythaemia rubra vera, and in eight cases radioactive colloidal gold has been introduced into the pleura or peritoneum for the management of recurrent malignant effusions.

WHAT IT ENTAILS FOR THE PATIENT

Investigation and treatment of patients with radioactive isotopes are relatively simple and far less unpleasant than many of the accepted lines of investigation in other spheres. Diagnostic procedures may be performed on outpatients, but when treatment is undertaken patients must be admitted and they should be kept in hospital until the amount of radioactivity present in them has fallen to 5 mc.

The isotopes are usually administered by mouth or intravenously, although occasionally they may be given by other routes: e.g. subcutaneously for measuring clearance of radioactive sodium from the skin of a pedicle graft. Those given by mouth are normally in aqueous solution and are quite tasteless. Patients, being human, often complain later that they felt sick or more nervous after administration, but as often they state that they felt much better and date the onset of their improvement from the time when the dose was given; this is all due to suggestion and the more phlegmatic patients notice no effects. A great deal can be done by simple explanation beforehand. X-ray diagnostic procedures and 'blood tests' are accepted

by patients as necessary evils and cause few qualms even though they may give considerable discomfort. Radioactive investigations, on the other hand, are new and it is understandable that there should be considerable apprehension.

External measurements with counters, either over the thyroid gland or other sites, cause no discomfort at all, though the patient may be required to lie still for half an hour. Neither is there any discomfort from the collection of urine although there may be some inconvenience, particularly for outpatients. After adequate explanation it is found quite satisfactory to have outpatients collect their urine and bring it back to the laboratory; in fact it is a general experience that these outpatient collections are far more likely to be accurate than those made in a busy general ward. Samples of blood or plasma may have to be taken and occasionally of other body fluids: e.g. pleural or peritoneal, but these are no more unpleasant to the patient than biochemical or hæmatological investigations and seldom will as many pricks be necessary as in a glucose tolerance curve.

Similar remarks apply to the therapeutic use of radioactive isotopes. For thyrotoxicosis one drink of a tasteless fluid containing radioiodine is given which causes no side-effects; for polycythæmia vera one injection of radioactive phosphorus, though both of these may have to be repeated later. The administration of radioactive colloidal gold into the pleural or peritoneal cavities should cause no more discomfort than the original removal of the fluid, although in this case there may be some anorexia and nausea for one or two days similar to that after conventional deep x-ray therapy.

In fact, one of the great advantages of these new techniques is their simplicity and the little disturbance they cause to the patient. Once the equipment and knowledge are available the relative ease and accuracy of the measurements make the use of radioactive isotopes a comparatively simple means of investigation. They will seldom supplant established methods in diagnosis, but they have already helped in the solution of many problems and it seems likely that many more uses will be found in diagnosis and research and, it is to be hoped, in treatment too.

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RADIOGRAPHY WITH RADIOACTIVE ISOTOPES

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THE naturally occurring radioactive materials such as radium have been used as radiographic sources from the earliest days of their discovery at the end of the nineteenth century. Since that time many industrial uses have been found for these x-ray emitters, as, for example, the detection of blow-holes and other flaws in metal castings.

In the field of medicine, however, the high penetrating power of these natural x-ray sources is far too great for radiography of the human body, both soft tissue and bone being traversed with almost equal facility. As a result of this no useful degree of contrast is registered on the photographic film. This situation, however, has been changed by the rapid post-war development of atomic physics, which has, amongst its many other achievements, made available a large number of artificial sources of x-radiation. Of these radioactive isotopes a few have penetrating powers low enough to produce satisfactory contrast as between bone and tissue.

Using one of these isotopes it is now possible to produce an extremely simple x-ray apparatus of such small weight and size that it can be carried around, together with a supply of films and cassettes, in a container little larger than a normal brief case. The apparatus is completely self-contained and requires no external power either from electricity mains or batteries. The possibilities of such an apparatus are many and varied. In field work, both military and civil, uses will at once come to mind, especially the examination of casualties. In the veterinary world also this type of apparatus may be of considerable value due to the ease with which it can be handled. Other uses already found include the radiography of old paintings and of porcelain figures.

To extend the usefulness of such an apparatus a portable film-developing outfit would be of great value and already a process has been developed by Picker-Polaroid, which has considerable possibilities in this field.

CHOICE OF SUITABLE ISOTOPES

We have seen that the primary requirement of a radioactive isotope for medical use is that its energy should be low enough to give good contrast; energies in the region of 50 kV have been found to be suitable. A secondary requirement is that the isotope should have a reasonably long half-life in order to avoid frequent replacement and recalculations of dose-rate as its strength decays. Two isotopes in particular have been investigated which

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to a large extent fulfil these conditions: thulium-170 and xenon-133. Thulium-170 is prepared from normal non-radioactive thulium-169 by placing it in the strongest available neutron flux of an atomic pile. The radioactive isotope is formed by neutron capture and proceeds to decay with a half-life of 127 days.

The decay scheme is complex (Mayneord, 1952; Mayneord and Ireland, 1956; Lidén and Starfelt, 1953) but, briefly, is by β -emission by two routes, one to stable ytterbium and the other to an excited state of ytterbium which emits γ -radiation of 84 kV and also its own characteristic x-radiation of 52 kV and 59.4 kV by a process known as internal conversion. In addition, there is a continuous broad band of bremsstrahlung radiation with a mean energy of about 150 kV. This is caused by the deceleration of the β -rays in the thulium, the mechanism being very similar to the production of x-rays in a normal x-ray tube.

Xenon-133, a gas, is a fission by-product of pile operation, it occurs in large quantities and has to be extracted by chemical and physical processes (Richards, 1955).

The decay scheme (Bergstrom, 1951) is by β -emission to caesium-133 which emits a γ -ray of 81 kV; this is internally converted and gives rise to x-radiation of 31 kV and 35 kV. No bremsstrahlung is present in the radiation from xenon-133.

For radiographic purposes it is well understood that for the highest definition we must have as near a point source as possible; this necessarily implies a high concentration of activity if the times of exposure are not to be excessive.

In the case of thulium-170 it has been possible to irradiate a disc of sintered thulium oxide, 2 mm. in diameter and 2 mm. thick, and reach an activity of several curies with dose-rates of up to 3 mr/minute at 30 cm. To prevent leakage of the active material and to absorb the unwanted β -rays the active disc is sealed into a light alloy capsule which is itself sealed into a second capsule, the total thickness of alloy being about 2.25 mm.

Xenon-133 radioactive sources are prepared by absorption of the gas on to charcoal at the temperature of liquid nitrogen (Richards, 1955); on reaching normal room temperatures it is found that most of the gas remains strongly absorbed.

Activities of one to two curies have been concentrated in charcoal grains of about 1.5 mm. in diameter. Sources of up to 13 curies have been made by absorbing the gas in a charcoal rod 1 mm. in diameter by 5 mm. long. The rod is sealed in a glass capillary tube and is viewed end-on in order to achieve small focal size. Such sources give dose-rates of up to 75 mr/minute at 30 cm.

APPARATUS FOR CLINICAL USE

For practical purposes the primary sources described above must be shielded and a suitable shutter mechanism arranged so that exposures can be made when required. The shielding must be adequate, so that when the shutter is closed the source is safe to handle; due to the low energy of the sources this is easy to attain. For both the thulium-170 and xenon-133 sources, of the above orders of magnitude, 0.6 cm. of lead is sufficient to reduce the dose-rate to less than the maximum permissible of 2 mr/hour at one foot from the source. Theoretically the best absorber is gold, especially of radiations in the region of 80 to 100 kV (Mayneord, 1952; Mayneord and

FIG. 2.-
hold
cass

Ireland, 1956); as little as 3 mm. of this material is sufficient for shielding purposes when the source strength does not greatly exceed the above figures.

It will be obvious that there are many simple methods of making a suitable shutter, the precise approach depending on the application in mind. One solution, designed for clinical use, is illustrated in fig. 1. It was

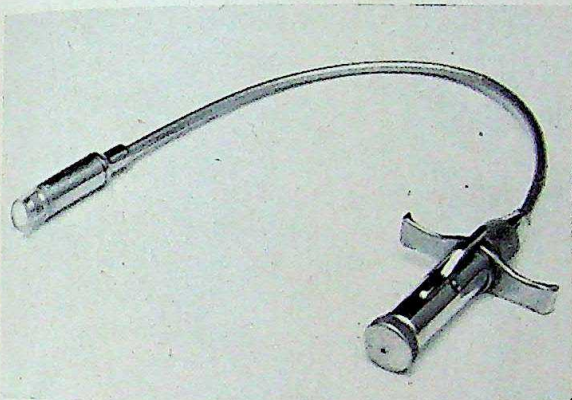
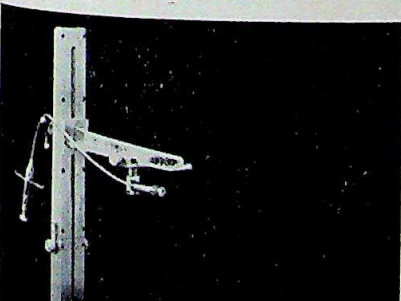


FIG. 1.—Gold-shielded clinical source holder.

originally intended to contain the double-sealed thulium-170 disc but it can easily be adapted to hold xenon-133 sources.

The dual capsule holding the thulium is connected to a Bowden cable leading to the operating plunger, the cable length being about 25 cm. The far end of the capsule is covered by a gold disc, 3 mm. thick, which in the closed position lies within the end of a gold cylinder of 3 mm. wall thickness. This gold cylinder is terminated

by a perspex dome into which the capsule and [its gold disc move when the plunger is operated. This is the exposed position and it will be seen that a 'lighthouse' beam or, more precisely, disc of radiation is emitted.



For normal use this source holder can be mounted on a stand such as that shown in fig. 2. This allows for variation of source-film distance and by sliding the source along the horizontal arm it can be centred over cassettes of various sizes. The illustration shows a 12 inch (30.5 cm.) \times 10 inch (25 cm.) cassette in position. The whole stand is

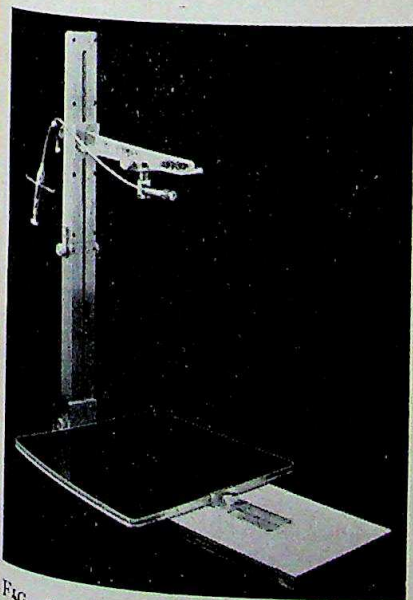


Fig. 2.—Gold-shielded clinical source holder on demountable stand, and cassette holder.

demountable and packs into a comparatively small space for transportation.

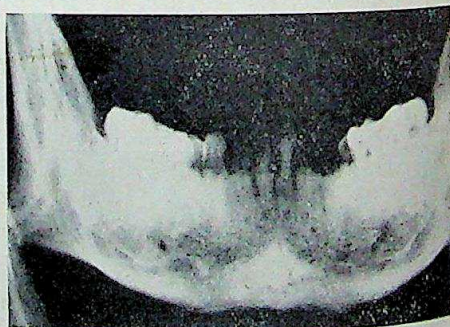
RADIOGRAPHIC EXPERIMENTS

The dose-rate from sources at present available does not approach that produced by conventional x-ray apparatus. As a result, we must use shorter focal distances and longer exposure times than in normal practice. To reduce the time of exposure to the minimum, fast films and intensifying screens are necessary and for this purpose we have used Ilford double-coated 'red seal' films and Ilford H.V. screens. For the type of work on which these sources are likely to be used the results are very satisfactory despite the loss of definition inherent in this combination of films and screens. A stationary Lysholm grid was tested with various objects but no improved definition could be demonstrated and the exposure times were doubled. A moving Bucky diaphragm resulted in a slight improvement but again at the expense of increased times of exposure.

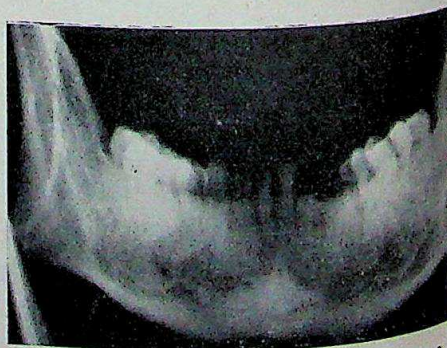
We have seen that thulium-170 sources have a bremsstrahlung component with a mean energy of about 150 kV. This comparatively hard radiation results in a noticeable loss of contrast; in this respect thulium-170 compares unfavourably with xenon-133 which has no significant radiation above 85kV. As the amount of bremsstrahlung present is directly related to the volume of thulium in the source, we should expect a small fragment of thulium-170 to give very much better con-



FIG. 3.—Radiograph of mandible of dried skull taken with a fragment of thulium-170 in mouth.



(a)



(b)

FIG. 4.—Mandible. Comparison of (a) x-ray and (b) thulium-170 radiographs.

trast than larger sources. That this is so can be seen by comparing the radiograph in fig. 3, taken with a small fragment, with that in fig. 4 (b), taken with a 2-mm. disc source. It is unfortunate that fragmentary sources

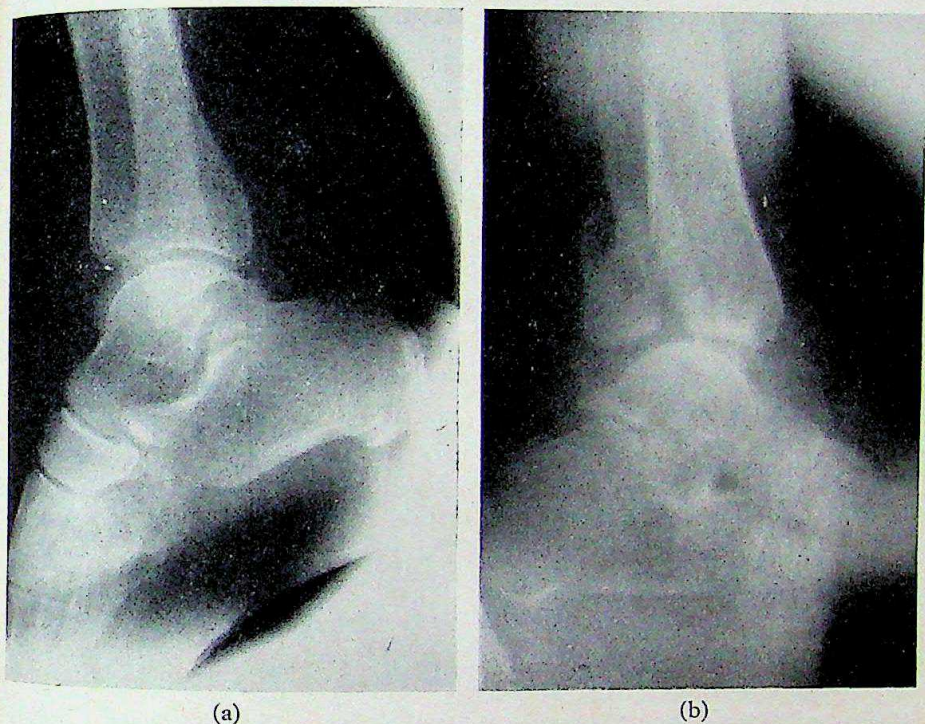


FIG. 5.—Xenon radiographs: (a) normal ankle, (b) fractured ankle.

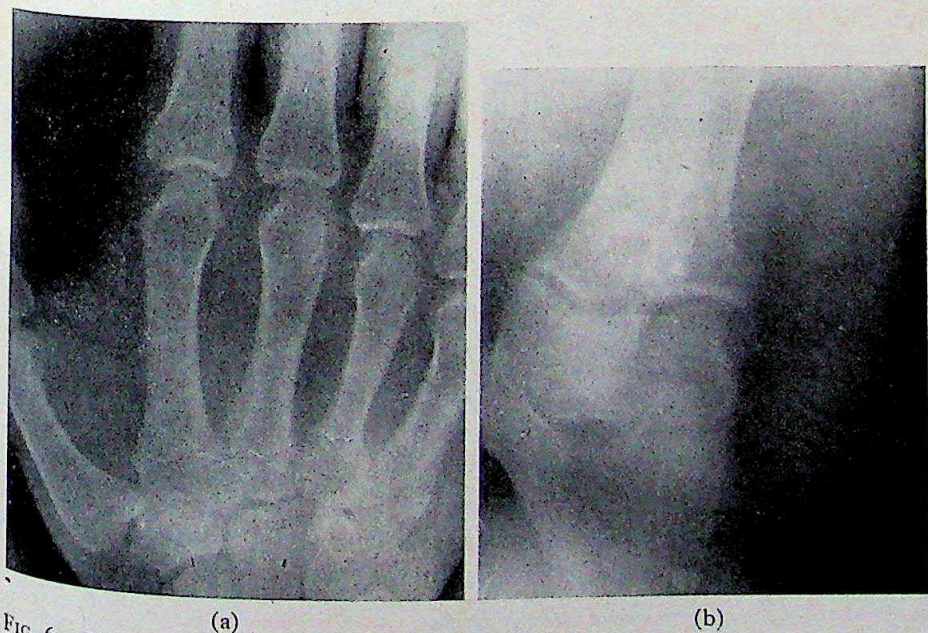


FIG. 6.—Xenon radiographs: (a) hand, exposure 3 seconds; (b) elbow, exposure 8 seconds.

cannot be produced with sufficient strength to give short exposure times; the radiograph of fig. 3 required an exposure of about 10 hours.

The presence of bremsstrahlung, together with the fact that thulium-170 is not such a safe material to handle, has led to the conclusion that xenon-133 is a more satisfactory source. Its disadvantage of a short half-life of 5.27 days can be set against the fact that due to the very large amounts available in atomic reactors it should be a simple matter to arrange for a supply of replacement sources at low cost. Some examples of radiographs made with xenon-133 are shown in fig. 5 and 6. The source used had an initial dose-rate of 70 mr/minute at 30 cm., this being the source-film distance at which most of these pictures were taken. It will be seen that radiography of the extremities is possible with exposures as short as 3 seconds when sources of this magnitude are employed. The radiograph in fig. 7 is included as one example of the many non-medical uses for these radioisotope sources.

A useful application would be in dental radiography, the method being to place the radioactive source in the centre of the mouth with the film wrapped round the outside of the face. Advantages would be orthogonal views of the full complement of teeth at one exposure instead of the many separate exposures required when using normal techniques. The source-film distances are of course very small, and this results in geometrical distortion from two causes; one due to the thickness of the teeth and the other to the finite size of the source. With sources of 2 mm. diameter the results have so far not been satisfactory but it is hoped that with a reduction to 0.5 mm. or less some useful results may be obtained. In this case the unavoidable reduction of source strength with size is offset by the short source-film distances.

A comparison of fig. 4 (a) and 4 (b), both of which were made with the same geometrical conditions and films, will make clear the difference in quality between thulium-170 and normal x-ray tube radiations. This difference is probably due to the continuous nature of the tube spectrum as compared with the mainly monochromatic line structure of the thulium-170. Here we may note that an x-ray tube at, say, 75 kV has an effective

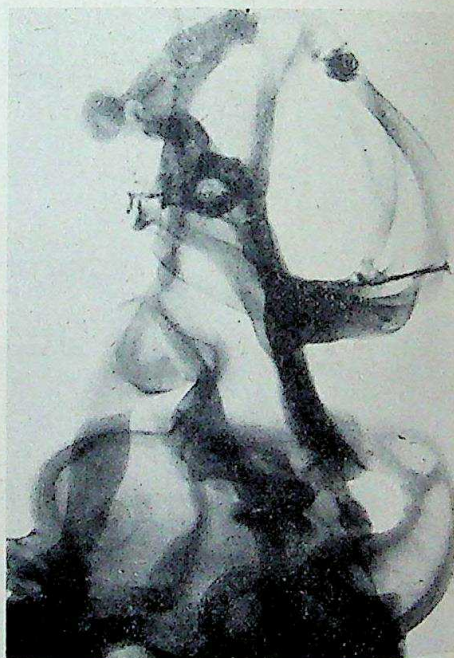


FIG. 7.—Radiograph of porcelain ornament taken with a fragment of thulium-170.

average radiation energy considerably above this, in the region of 100 to 120 kV. Nevertheless, in spite of this poorer quality, radioactive isotopes, whilst not suitable for fine detail examination, have shown that for gross changes, e.g. dislocations and fractures, they may have a useful role to play in human radiography.

HAZARDS

We have seen that the radiation from these isotopes is easily screened and reduced to a safe level. There is, however, a serious risk from accidental ingestion of the active material. Thulium-170 is generally produced from sintered thulium oxide so that the possibility of some of the powder escaping from its capsules must be guarded against. Thulium-170 is a bone-seeker with an effective biological half-life of 60 days, the maximum safe body burden is only 4 microcuries (recommendations of the International Commission on Radiological Protection, 1955). This amounts to less than 0.1 micrograms of the material, underlining the need for perfect sealing. From this point of view it would be better to use the metal instead of its oxide (Untermeyer *et al.*, 1954).

Xenon-133 is less dangerous because of its short half-life, the maximum permissible air concentration is 4×10^{-6} microcuries/ml. and the maximum body burden is 320 microcuries (Tobias *et al.*, 1949). A further safeguard is the fact that, in common with the other rare gases, it is chemically inert and not easily absorbed in the body.

This account is possible due to the early interest taken in the subject by Professor W. V. Mayneord, the director of the department of physics, and to the work he has devoted to the subject in the last few years. The sources have been made available due to the kindness of many friends in the British and Canadian Atomic Energy Establishments. Dr. M. W. Wood of the x-ray diagnostic department of the Royal Marsden Hospital has given great assistance in the clinical aspects of the work.

Figures 1, 2, 4, 5 and 6 are reproduced from the *British Journal of Radiology*, and figure 3 from *The Lancet*, by kind permission of the Editors.

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THE PHYSICAL BASIS OF HEADACHE

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'I shall therefore commend to you the study of symptoms for their own sake as well as for the sake of your patients and your professional reputations'.—J. A. Ryle (1936).

HEADACHE is one of the most common symptoms encountered in clinical medicine, and one of the most troublesome. It is therefore a little surprising that it is almost ignored in medical teaching and writing in this country; the more so because much has been learned about it in the last two decades, and there is now a considerable body of established anatomical and physiological facts relating to it, much of which is of practical value and interest to the clinician. This article is an attempt to outline this knowledge and to indicate its clinical relevance.

PAIN

Headache is essentially pain in the head, and some knowledge of the physiology of pain and the anatomy of the head are essential to a proper understanding of it.

Pain is a subjective sensation which evades definition: let it suffice to say with Lewis (1942) that it 'is known to us by experience and described by illustration'. It is a specific and independent modality of sensation like heat, cold and touch (Adrian, Cattell and Hoagland, 1931). Pain receptors are plain bare nerve-fibrils; in the skin they are excited by a wide variety of stimuli such as pricking, cutting, burning, pinching, and the application of caustic chemicals, but in other tissues the range of noxious stimuli is smaller; for instance, the intestinal wall probably responds only to stretching and ischæmia (though the evidence on this point is not wholly conclusive [Kinsella, 1948]). Skin, as befits its protective function, is liberally provided with pain receptors, but deeper tissues have fewer, and some, such as the brain and bone marrow, none at all.

Pain arising in the skin is well localized, promptly felt, and has a quality described as pricking or burning; that arising from deeper structures is less well localized, less urgent, and is described as dull, aching or throbbing; it tends to give rise to false localization by reference, spread and muscle spasm, and to evoke autonomic accompaniments such as sweating, bradycardia, and nausea (Lewis, 1942).

Pain impulses from the skin (and probably elsewhere) reach the central nervous system via two sorts of fibres: some thin and poorly myelinated with a slow rate of conduction, others thicker and well-myelinated with a rate of conduction about twenty times as great (Bigelow *et al.*, 1945; Gasser, 1934). It is of some interest that those impulses which originate nocifensor reflexes (such as the instantaneous withdrawal of an injured limb, before the hurt is properly appreciated by consciousness) April 1957. Vol. 178

travel by the thicker, more rapidly conducting fibres, and it is these that are chiefly damaged in a disease such as tabes dorsalis.

Pain-fibres of both sorts enter the spinal cord by the posterior root and relay in the grey matter of the posterior horn (and also communicate with neurons in neighbouring segments, especially those cephalad); second-stage fibres cross the cord to ascend in the lateral spino-thalamic tract to the posterior ventral nucleus of the thalamus. At this point the sensation of pain

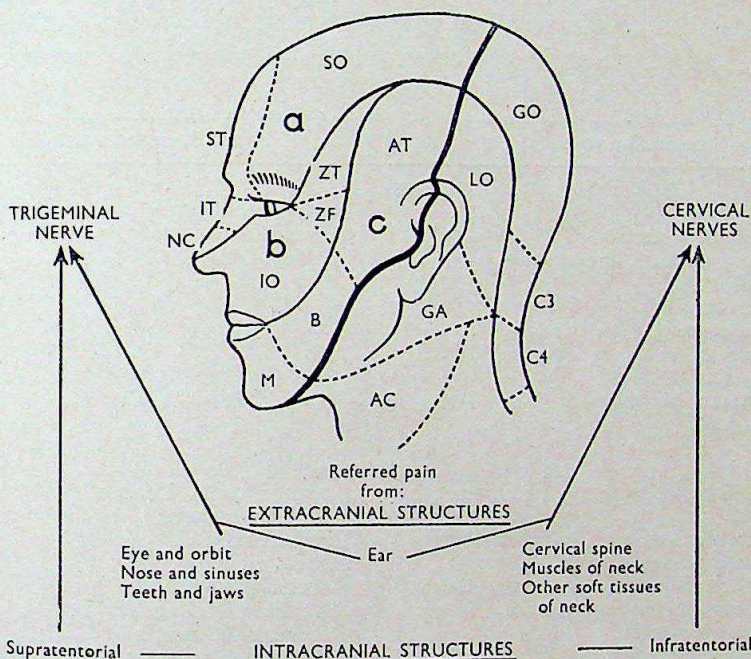


FIG. 1.—Cutaneous innervation of the head, and main areas of reference of pain arising in deeper structures.

Abbreviations:

- a . . . 1st (ophthalmic) division of trigeminal nerve.
- b . . . 2nd (maxillary) " " " "
- c . . . 3rd (mandibular) " " " "

Branches of trigeminal:

- a: supraorbital (SO), supratrochlear (ST), infratrochlear (IT), nasociliary (NC).
- b: zygomaticotemporal (ZT), zygomaticofacial (ZF), infraorbital (IO).
- c: auriculotemporal (AT), buccal (B), mental (M).

Branches of cervical nerves:

- anterior primary rami: lesser occipital (LO), great auricular (GA), anterior cutaneous of neck (AC) (all from C2-3);
- posterior primary rami: greater occipital (GO), and P.P.R. of C3, C4, etc. (GO from C2).

enters consciousness, but there are intimate connexions between the thalamus and postcentral convolutions of the cortex, described by Walker (1943); these probably serve to amplify the basic thalamic pain-sensation and coordinate it with other afferent stimuli, and also to modify the primitive thalamic responses to pain such as the 'sham rage' and 'sham grief' seen in decorticate animals and occasionally in human patients with lesions in the thalamic region (Cannon, 1929; Goltz, 1892).

Pain-fibres from the trigeminal nerves relay in the spinal or descending

root of the nerve, those from the ophthalmic division in the lowest part, the maxillary in the intermediate part, the mandibular in the uppermost; second-stage fibres then cross to the other side of the brain-stem to ascend in the thalamus in close company with the spino-thalamic fibres.

NEUROLOGY OF THE HEAD

Table I shows that, whilst most extracranial structures are pain sensitive in varying degrees, this is not true of the cranium itself or its contents. It is noteworthy that the brain and much of the meninges are insensitive, and

Sensitive to pain	Insensitive to pain
EXTRACRANIAL	
Skin Subcutaneous tissue Muscles, tendons, aponeuroses Arteries Nerves (usually) Orbital contents Mucosæ of oronasal cavities, middle ear, etc. Periosteum, pericranium Teeth, jaws	Superficial veins Cranial bones Diploë
INTRACRANIAL	
Dural floor of anterior and posterior fossæ Dural venous sinuses, and dura in their immediate vicinity Large arteries at base of brain, and their larger branches for a variable distance from their origin Meningeal arteries, and dura in their immediate vicinity Cranial nerves V, VII, IX, X, XI, XII	Dura of vault, floor of middle fossa, falx, tentorium Pia-arachnoid Ependyma Choroid plexuses All other blood vessels Other cranial nerves Parenchyma of brain

TABLE I.—Pain-sensitivity of structures and tissues of the head. No attempt is made to indicate degrees of sensitivity. This table is based for the most part on data from Wolff (1948), supplemented from many other sources.

by far the most important intracranial pain-sensitive structures are the larger blood vessels and the dura in their immediate vicinity.

Figure 1 shows the superficial sensory innervation of the head, and also indicates in a broad way the areas to which pain is referred from various intra- and extra-cranial sites. It will be seen that the trigeminal nerves are responsible for most of the head anterior to the ears, and the supratentorial cranial contents; the posterior part of the head is innervated by the second and third cervical nerves, and infratentorial structures by the last four cranial and first three cervical nerves.

REFERRED PAIN

Pain caused by noxious stimulation, especially of a deep structure, is often felt in another region of the body whose sensory innervation is derived from the same segment (Lewis, 1942). Although the precise mechanism of pain

reference is still a matter of controversy, clinical examples are legion: for instance, pain in the shoulder in diaphragmatic pleurisy (both regions being innervated by the fourth cervical segment, via branches of the cervical plexus and the phrenic nerve, respectively).

Referred pain plays an important part in headache, and most if not all headache from intracranial causes is referred. Wolff (1948) and others have

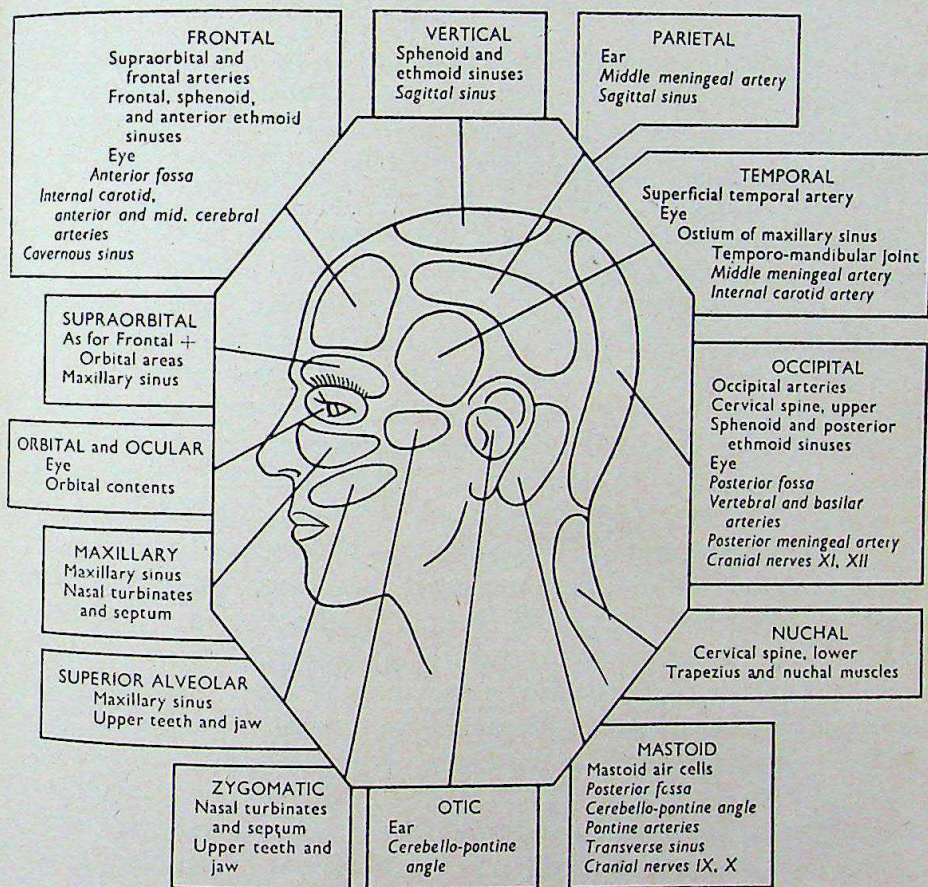


FIG. 2.—Approximate areas of reference of pain arising in some of the more important intracranial and extracranial situations. Intracranial structures are designated by italics.

worked out with much ingenuity the areas of reference of pain arising in a great number of intra- and extra-cranial situations, some of the more important of which are shown in figure 2.

SPREAD OF PAIN

Kunkle and Armistead (1948) showed that if the middle finger is immersed in ice-cold water it becomes painful, and that after a while the pain appears to spread to the adjacent fingers: this spread is neither prevented nor relieved by local anæsthesia of the adjacent fingers, because it is central and not peripheral in origin. The persistent flow of afferent stimuli into neurons

concerned with pain sensation in the immersed finger 'overflows', so to speak, via communicating fibres of the dorsal horn and association fibres in the white matter of the cord to neighbouring neurons in the same and adjacent segments. This central diffusion is especially important in pain arising from deep structures, and plays a considerable part in the production of headache in disorders of extracranial structures such as the eyes, sinuses and teeth.

PAIN OF MUSCULAR ORIGIN

Lewis and Kellgren (Lewis, 1942) showed that persistent noxious stimulation of a structure causes tonic contraction of muscles innervated from the same segment, with pain and tenderness in the muscles in due course. The phenomenon is familiar enough in the fixation of a painful joint, or the rigidity of the abdominal wall over a patch of peritonitis. It is somewhat less familiar in the form of temporal pain and tenderness from spasm of the temporalis muscle in disease of the temporo-mandibular joint, parotitis, or malocclusion; or occipital headache associated with disease of the upper cervical spine, or posterior cervical lymphadenitis. Spasm of the muscles of the scalp and forehead, the nape, the temple, the sternomastoid and ocular muscles, may in fact be provoked by a wide variety of painful conditions about the head and neck: for example, ocular disease, neuralgia, toothache, sinusitis, lymphadenitis, cervical spine disease, meningeal irritation, and the effects of trauma. In addition, headache from any cause, such as migraine, may be intensified, spread and prolonged by reflex muscle spasm.

Painful spasm may also be brought about by disorders of the muscles themselves, the commonest being muscular rheumatism (or 'fibrositis'), a frequent cause of mild, persistent headache, especially in the occipito-nuchal region. Auerbach, in 1913, emphasized the importance of this form of headache, yet even today it is commonly overlooked.

The typical headache of emotional tension is largely or entirely muscular in origin, and Sainsbury and Gibson (1954) have shown electromyographically that the onset of such a tension headache is accompanied by an increase in electrical activity of the scalp muscles. Wolff (1948) considers that the persistent deep suboccipital ache so common in hypertension is also muscular. Postural or occupational headaches in typists, car-drivers and others are further examples of entirely or predominantly muscular headaches.

Simons and Wolff (1946) demonstrated that many chronic post-traumatic headaches are of muscular origin; they may be localized to the traumatized area or scar, or generalized, but in either case demonstrate the general clinical features of muscular headache, which are:—

- (1) Low to moderate intensity, often a feeling of pressure or vague discomfort rather than pain.
- (2) Persistence, opposed to the paroxysmal nature of most vascular headaches.
- (3) Clinically detectable spasm and tenderness of the involved muscle masses, with aggravation of the headache by firm palpation of these or of 'trigger points' therein.
- (4) Electromyographic evidence of increased activity in the affected muscles.

(5) Relief, perhaps only temporary, following the abolition of spasm with the aid of physiotherapy, muscle relaxants such as mephenesin, or infiltration with procaine.

ARTERIAL HEADACHE

When a normal person is given an injection of histamine, after a brief interval he experiences a throbbing headache lasting a few minutes. This histamine headache has been carefully studied by Pickering and Hess (1933) and others, and has the following important characteristics:

(1) It is relieved by lowering the blood pressure in the branches of the internal carotid artery (e.g. pressure on the internal or common carotid in the neck); or raising the cerebrospinal fluid pressure (e.g. intrathecal injection of fluid, or pressure on the internal jugular vein).

(2) It is aggravated by procedures having the opposite effects (e.g. coughing, straining, and withdrawal of cerebrospinal fluid); and by shaking or jolting the head.

(3) The throbbing of the pain is synchronous with the carotid pulse.

(4) At craniotomy the headache is seen to be accompanied by dilatation and increased amplitude of pulsation of the cerebral (but not meningeal nor extracranial) arteries.

(5) The headache is most severe when the blood pressure has returned to near normal after its preliminary fall, but the cerebral arteries are still hypotonic and dilated.

These and other observations indicate that the headache is caused by stretching of periarterial nerve plexuses of cerebral arteries through excessive amplitude of pulsation: or, to put it another way, by the shock of systole impinging upon a hypotonic and imperfectly supported arterial wall.

There is evidence that the headaches of fever, the alcoholic hangover, anoxia, concussion, and that produced by vasodilators such as the nitrites, are similar in mechanism to the histamine headache; a related variety is that which occurs with a sudden lowering of cerebral arterial blood pressure from such a cause as the rapid assumption of the upright posture in certain predisposed persons (Kunkle, Lund and Maher, 1948; Marmion, 1956).

Migraine, in contrast to histamine headache, is for the most part a disorder of the external carotid system of arteries. The temporal, or sometimes the occipital, artery on the affected side can indeed be seen to be dilated and pulsating forcibly during an attack, the pain being relieved by partly occluding the artery by digital pressure near its origin, or by pressure on the external carotid in the neck; but if the attack persists for long the arterial wall becomes œdematous and these procedures bring little or no relief. Intracranial vessels are also involved in migraine, for the aura is caused by constriction of cerebral vessels and may be terminated by prompt inhalation of amyl nitrite (Shumacher and Wolff, 1941). Moreover, there is evidence that in some cases at least intracranial arteries are partly responsible for the pain. Ergotamine is a powerful constrictor of branches of the external carotid system, and this accounts for its efficacy in relieving the migraine headache, as demonstrated by Lennox and von Storch (1935); alone or in combination with caffeine it will abort or greatly relieve over 80 per cent. of cases.

Sutherland and Wolff (1940) have shown that the common headache of

arterial hypertension (but not that of hypertensive encephalopathy) resembles migraine in its causation. Many of the so-called 'atypical facial neuralgias' (Campbell and Lloyd, 1954), including Horton's histamine cephalgia (Horton, 1940) and Sluder's 'lower-half headache' (Sluder, 1908), are also nowadays considered to be autonomic and vasomotor disturbances related to migraine. A large number of common everyday headaches are of arterial origin, both intra- and extra-cranial vessels being involved in varying degrees.

The foregoing types of arterial headache may be considered physiological because the arterial changes are brought about by physiological agencies and are ephemeral and reversible: in contrast are arterial headaches due to irreversible, permanent or progressive changes such as aneurysms, angiomas, arteritis and degenerative conditions. It would take too long to discuss these here, and the interested reader is referred to standard up-to-date neurological textbooks and monographs.

INTRACRANIAL SPACE-OCCUPYING LESIONS

In 1913, referring to the headache of cerebral tumour, Auerbach said: 'There can be no doubt that it is the pressure [of cerebrospinal fluid] as such which produces a powerful irritation of the nerves of the dura mater'. Thirty-five years later, Wolff and Wolf (1948), writing on the same topic, could say that 'increased intracranial pressure is neither a prime nor an essential factor'. It has in fact been well established that pain occurs only when the lesion directly or indirectly causes displacement or distortion of the larger blood vessels or other pain-sensitive structures within the skull (Ray and Wolff, 1940). This explains why greatly raised intracranial pressure can be present without headache, whilst a small tumour or aneurysm causing little or no increase in pressure can, nevertheless, give rise to severe headache. Furthermore, a leak of cerebrospinal fluid (with a *decrease* in pressure) after lumbar puncture can permit a slight but massive displacement of the whole of the cranial contents with consequent traction upon their pain-sensitive anchorages, causing severe headache.

These facts also indicate why the site of the pain is often of poor localizing value in intracranial tumour, since the structure whose distortion causes pain may well be at some distance from the tumour, even in a different cranial fossa or on the opposite side; for the distortion may not be due to the tumour mass itself, but to oedema or ventricular distension caused by interference with the circulation of blood or cerebrospinal fluid. Nevertheless, Wolff and Wolf (1948) make some helpful generalizations about the localizing value of headache in tumour:—

- (1) In the absence of papilloedema, if the headache is unilateral it is likely to be on the side of the tumour.
- (2) Pain initially or entirely at the back of the head indicates a posterior fossa tumour.
- (3) In the absence of papilloedema headache in the front of the head suggests a supratentorial tumour.

- (4) If headache is both frontal and occipital it is of little localizing value.
- (5) The situation of headache in the earlier stages of the history may be of localizing value, when in the later stages the headache has become more diffuse.

HEADACHE DUE TO MENINGEAL IRRITATION

The meninges are sensitive to irritation by infection and by foreign substances such as blood and air. Examples of headache from these causes are those of meningitis, subarachnoid hæmorrhage, and pneumocephalography, respectively. It is apt to be severe and accompanied by symptoms and signs which are generally recognized as indicative of meningeal irritation: to wit photophobia, irritability, restlessness, nuchal muscle spasm and head retraction, nausea and vomiting.

NEURALGIA, NEURITIS AND NEUROGENIC PAIN

The common neuralgias, such as trigeminal and glossopharyngeal, do not give rise to true headache except by provoking secondary muscle spasm.

Any nerve may be the seat of neuritis from a variety of causes, and neuritis of the supraorbital, occipital, and auriculotemporal nerves, for example, may cause headache both of itself and through reflex muscle spasm. Infection of the posterior root ganglia (and their cranial homologues, especially the Gasserian and geniculate ganglia), as in herpes zoster and tabes dorsalis, also causes pain of neuritic character; post-herpetic neuralgia in various situations about the head is not uncommon in the elderly.

Pressure upon nerves or roots may cause pain, as in the occipital headache that may be caused by orthopædic conditions of the upper cervical spine; whilst the divisions of the trigeminal nerve are especially apt to be affected by aneurysms and other masses in the neighbourhood of the cavernous sinus. A neurofibroma in the course of a nerve of the scalp is an occasional cause of headache.

Disorders of the pain pathways, the spino-thalamic and quinto-thalamic tracts and the thalamus, must be mentioned for completeness, but are rarely causes of headache.

HEADACHE OF PSYCHOLOGICAL ORIGIN

Headache of psychological origin is one of the commonest conditions in medicine: it is an almost invariable symptom of anxiety neurosis and tension states, it is common in hysteria, depression, and psychopathic personality, and also occurs in obsessional states, schizophrenia, and many organic dementias.

Muscular tension headache has already been considered, and may be regarded as a by-product of the increased muscle tone that is part of the instinctive reaction to danger and stress. Vascular headache of emotional origin is probably equally common, but less easily explained, although a simple pressor headache may be caused in some persons by the release of adrenaline at times of stress. Cannon (1929) showed how emotions such as

fear and rage, acting on autonomic centres in the hypothalamus, prepare the body for violent activity—'fight or flight'—by, amongst other adjustments, vasomotor changes bringing about redistribution of blood; he also observed that 'if no action succeeds the excitement, and the emotional stress . . . persists, then the bodily changes due to the stress are not a preparatory

Mechanism	Physiology	Familiar clinical example	Example of headache
Direct	Pain felt at site of noxious stimulus.	Pain of pricked finger felt at site of prick.	Temporal headache in temporal arteritis.
Referred	Pain referred from site of noxious stimulation to another site of similar segmental innervation.	Pain in the shoulder in diaphragmatic pleurisy (both C4).	Supraorbital headache in internal carotid aneurysm (both trigeminal).
Spread	Noxious stimulus causes excitation of sensory neurons in posterior horn with 'overflow' of excitation to other neurons in same and neighbouring segments, so that pain appears to spread to regions innervated by those neurons.	Crush injury of one finger causes pain in adjacent fingers also (cervical and thoracic segments).	Toothache in upper jaw may spread to cause faceache and headache (trigeminal).
Muscular	Noxious stimulus causes reflex spasm of muscles innervated by involved segment; persistent spasm causes pain and tenderness.	Pain, tenderness and spasm of loin muscles in renal disease (thoracolumbar segments).	Occipital headache in upper cervical arthritis (C2-3).
Neurogenic	Disorders of neural paths and centres subserving pain sensation (i.e. nerve, posterior root and ganglion, posterior horn, spino-thalamic tract, thalamus; and homologous cranial nerve structures and connexions).	Neuritis, neuralgia, tabetic lightning pains, thalamic syndrome.	Occipital, supra-orbital, etc., neuralgia.
Psychogenic	Pain exists only in sensorium (i.e. is 'suprasegmental').	'Cardiac' pain in effort syndrome.	Some kinds of hysterical headache.

TABLE II.—Pain mechanisms and pathways.

safeguard but may be in themselves profoundly upsetting to the organism as a whole'. This is perhaps still the nearest approach we have to an explanation of the emotional origin of vasomotor headache.

The types of headache just described are sometimes called *physiogenic* in contrast to the strictly *psychogenic* headache, in which the pain exists only in the sensorium and has no physical basis at the periphery. This sort of headache is far less common than is often supposed, even in hysteria.

Indeed, Weiss and English (1949) go so far as to say that 'in the last analysis, no headache is imaginary: emotions are quite capable of producing true headache, by their repercussions in the muscles or vessels from which the painful sensations arise'. Clinical experience suggests that truly psychogenic headache often co-exists with physiogenic, emphasizing and exaggerating it—constituting, one might almost say, the familiar 'overlay'.

PAIN MECHANISMS IN HEADACHE

We have now considered briefly the mechanisms by which pain in headache may be produced: these are summarized in Table II. It must be clear that by far the most important sites of origin of the pain are the arteries and the muscles; the latter must especially be emphasized, not only for their importance as prime causes of headaches, but for their ubiquitous presence as causes of intensification, spread and prolongation of pain by reflex spasm. A great many headaches from all causes have an important muscular component which may obscure the real origin. Moreover, even when the underlying primary headache is resistant to treatment, a useful degree of symptomatic relief may be obtained by treating the muscular component by relatively simple physical measures.

It will be understood that pain may be felt in situations other than its site of origin, or may appear to spread peripherally from that site, for several reasons: to wit, segmental reference, central spread, and reflex muscle spasm. The neurology of the head is exceedingly complex, and the interplay of these mechanisms is all too often bewildering as well as fascinating in its infinite variety.

HEADACHE DUE TO DISORDERS OF EXTRACRANIAL STRUCTURES

It would take too long to describe in detail the parts played by the eyes, orbital contents, nose, sinuses, pharynx, jaws, teeth, ears, skull, cervical spine, and soft tissues of the head and neck in the etiology of headache, but a few words may be said to amplify the general principles already discussed.

The sensory innervation of the eyes and orbits is by the trigeminal nerves, and pain arising in them is either felt locally or spread or referred in the trigeminal area, especially in the territory of the first division. Muscular spasm and pain are prominent features of ocular disorders, the affected muscles being the obvious ones (the frowning muscles—orbicularis oculis, procerus, frontalis—and the extrinsic and intrinsic ocular muscles), and the less obvious nuchal muscles. The last are involved because the eyes are closely linked with the complex neurological mechanisms for the maintenance of posture, and the extrinsic ocular muscles have close connexions with the neck muscles via the posterior longitudinal bundle. The whole interesting topic of the relation of eyestrain and ocular disease to headache is admirably set forth by Duke-Elder (1949).

The nose and sinuses also lie for the most part in the trigeminal area,

and pain arising therein is usually referred to the front half of the head, although disease of the sphenoid and posterior ethmoid sinuses may cause vertical, occipital and nuchal pain. Sinus pain tends to be remarkably constant in its time-relationships, recurring and passing off punctually the same time every day in a given patient. It may be said, in passing, that sinusitis is greatly overrated as a cause of headache. In contrast, dental disease is apt to be underrated: malocclusion (Costen, 1936) and many other disorders may be responsible for puzzling temporal headache, probably from spasm of the temporalis muscle.

The sensory innervation of the ears is complex, involving the Vth, VIIth, IXth and Xth cranial nerves, so that the possible area of pain reference is wide; nevertheless, pain arising in the ear is most often felt simply as earache, with or without headache from spread or pain or muscle spasm. Mastoid pain may arise from local disease such as mastoiditis, from a lesion in the cerebello-pontine angle (e.g. an acoustic neuroma) or posterior fossa, and also from spasm of the upper part of the sternomastoid muscle, most often caused by adjacent lymphadenitis.

Disorders of the cervical spine and neck musculature are common causes of headache, especially occipital and nuchal; the pain may spread forward to the vertex, temples and forehead, or may extend down the back or out to the shoulder.

CONCLUSION

I have described briefly the anatomical and physiological basis of headache, the immediate means by which pain is caused and perceived, so far as they are understood. This may usefully and accurately be called the *proximate cause* of headache; it is only part of the story, for there is always an *ultimate cause* as well. For instance, the proximate cause of a 'hangover' headache is cranial arterial pulsation, the ultimate cause over-indulgence the previous night; the proximate cause of headache in a case of intracranial tumour is traction upon pain-sensitive structures, the ultimate cause the growth itself; the proximate cause of a muscular tension headache is persistently increased muscle tone, the ultimate cause emotional tension. And so on. The ultimate cause must always be the diagnostic goal, for only when it is identified and put to rights is it permissible to speak of cure. A knowledge of proximate causes, however, and the part they play helps materially in the search for ultimate causes, provides a rationale for symptomatic treatment when the ultimate cause is inaccessible to diagnosis or refractory to treatment, and renders the whole subject more coherent and comprehensible.

The link between ultimate and proximate causes in the realm of psychosomatic disorder (which embraces the vast majority of headaches) is obscure, despite researches and conjectures by an army of workers on the relation of stress to disease (Wolff, 1953). We know that a certain person has periodic vasomotor headaches of a type we call migrainous, and we therefore say that he has a 'migrainous diathesis': knowing this, we can forecast that if he is subjected to certain strains and stresses he will have more frequent and

more severe headaches. But why does he have headache at all, when in similar circumstances another person might have dyspepsia, another neurodermatitis, and another hypertension? We can give no better reply to this question than Kessel (1930) did twenty-five years ago: that in a given individual a definite reaction picture develops in response to a given emotion. But this is merely talking in a circle.

There is much therefore to be learned about headache; yet if the light shed by recent clinical and experimental studies has not dispersed the darkness, it has at least enabled us to discern a coherent pattern in the scheme of things which we cannot afford to ignore, for the reasons given by the late Professor Ryle in the quotation at the beginning of this article.

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THE VALUE OF ELECTRO-CONVULSIVE THERAPY IN THE NEUROSES

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ELECTRO-CONVULSIVE therapy (E.C.T.) is the most extensively used method today in the treatment of mental disorders, and it has application over a wide range of conditions. Although it is primarily used in the affective psychoses, it is also often employed in the treatment of the neuroses, and, in general practice, conditions such as the milder melancholias and schizoid personalities may be conveniently grouped with the true psychoneuroses (e.g. anxiety states, hysterias, obsessive-compulsive conditions). These form a high proportion of the mental disorders seen and treated outside a mental hospital, and it is the purpose of this article to determine the long-term effect of E.C.T. in these conditions, and to evaluate some factors of prognostic importance.

SCOPE OF INVESTIGATION

The material was taken from the neurosis unit in a general hospital, where both inpatients and outpatients are treated. One hundred unselected patients, who had been treated with E.C.T. by the same investigator, were written to after two to four years had elapsed since treatment. They were asked to re-attend for interview, but those who could not attend were requested to return a questionnaire which asked whether the patient's nerves were now well, if there had been any relapses since treatment, if the patient was working, whether their own doctor was still being attended for nerves; in addition, there was a space for further remarks. Eventually, 77 replies were received, and, of these, 28 attended for personal interview.

Of the total, 34 (44.2 per cent.) were males and 43 (55.8 per cent.) were females. In general, the ages ranged from twenty to sixty years, only three being below twenty years (16, 17 and 18 years) and two over sixty years (both 61 years). Nineteen (24.7 per cent.) were treated as outpatients and 58 (75.3 per cent.) as inpatients, and an average of just over three years had elapsed between treatment and subsequent reassessment.

RESULTS

Fifty-seven, 74.1 per cent. of the total, were found to have remained quite fit ('recovered' group) and the remaining twenty (26 per cent.), who still had nervous symptoms, were therefore classed as 'failures' from the treatment point of view. It should be noted, however, that 13 (65 per cent.) of these 'failures' were working.

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Immediately following treatment, the following effects had been noted:—

In the 'recovered' group,

32 (56.1 per cent.) were discharged as 'recovered'

14 (24.6 per cent.) were discharged as 'improved'

11 (19.3 per cent.) showed no immediate change.

In the 'failure' group,

Five (25 per cent.) were discharged as 'recovered'

Six (30 per cent.) were discharged as 'improved'

Nine (45 per cent.) showed no immediate change.

Fifty (65 per cent.) of the total no longer attended their own doctor, and of the remaining 27 who did, many only continued a sedative or placebo habit. Nineteen (95 per cent.) of the 'failure' group, compared with 40 (70 per cent.) of the 'recovered' group, were treated as inpatients.

The 26 'failures' (26 per cent.) were then compared with the 57 'recoveries' (74 per cent.) from various standpoints, and the results are summarized in table I.

	'Recoveries'	'Failures'
Evidence of previous mental breakdown or familial mental instability	49.4%	60%
Duration of symptoms:—		
Less than 3 months	7.8%	5%
Between 3 and 12 months	32.5%	30%
Over 12 months	59.7%	65%
Diagnoses:—		
Anxiety states	39%	45%
Predominantly depressive states	23.4%	15%
Schizoids	15.6%	15%
Hysterical conditions	11.7%	10%
Psychopaths	3.9%	10%
Obsessional neuroses	2.6%	5%
Miscellaneous	3.9%	
Average number of E.C.T.s per patient	4.4	4.05

TABLE I.—Comparison of findings in patients who showed a lasting response to electro-convulsive therapy and in those who did not.

DISCUSSION

Before drawing any conclusions from these figures, there are other factors to be borne in mind. Many neurotics may be improved by any form of enthusiastic medical approach, particularly if it involves admission to hospital. The fact that 95 per cent. of the 'failures', compared with 70 per cent. of the 'recoveries', were treated as inpatients, however, suggests that the hospital regime alone did not contribute materially to recovery. From the point of view of the direct effect of treatment, it will be seen that 80 per cent. of the 'recoveries' showed an immediate response, as also did 55 per cent. of the 'failures'. Thus, over half of the 'failures' showed a transitory

improvement, which might have engendered undue optimism for the treatment had they not been assessed after an appreciable interval. On the other hand, 20 per cent. of the 'recoveries' showed no immediate response, so their subsequent improvement must have been due either to a delayed response to treatment (an effect which is well known) or, in some cases, to the influence of other factors. Sixty per cent. of the 'failures' showed evidence of constitutional instability, but this was also appreciable (nearly 50 per cent.) in those who remained well after approximately three years. When the duration of symptoms is examined, there is no material difference between the two groups, and it is significant that even in the recovered groups nearly 60 per cent. had had symptoms previously lasting over twelve months.

Although this does not fully support the opinions of several authorities upon the adverse effects of constitutional factors, and the long duration of symptoms before treatment, quoted by Monro and Conitzer (1950), it will be observed that these factors were present in a high proportion of the original total group and hence may appear to be excessively represented in the 'recovered' group.

In considering the effects in the different diagnoses, the important question is raised as to whether many of them were really primary emotional disorders. Against this, apart from their presenting symptomatology, is the predominance of the long duration of symptoms, which is unusual in affective syndromes. In discussing the effect of E.C.T. on the depressive states Karagulla (1950) claimed that approximately 30 per cent. had to be re-admitted within two to five years of being discharged 'recovered' or 'improved' after E.C.T., and suggested that this was not substantially different from that of a control group who did not have E.C.T. Although her statistical inferences were subsequently criticized by Slater (1951), it is probable that a proportion of our 'recoveries' would have occurred without treatment, albeit more slowly. It is significant, however, that several of our patients spontaneously remarked subsequently that the treatment marked 'the turning point' or that they had 'never felt better than in the years following treatment'.

It will be seen that the anxiety states, schizoids and hysterics are represented by approximately equal percentages in our two groups, and it may be assumed that in the 'recovered' group the depressive component was more marked. As Sargant (1951) states: 'I have never seen good results from E.C.T. in anxiety states, obsessional neurosis or hysteria, unless there was a depressive component, and, even then, results are not comparable to those achieved in the retarded depressions'. Our predominantly depressed states, although representing 23 per cent. of the 'recoveries', also comprised 15 per cent. of the 'failures', but, as our 'failures' were assessed after a prolonged period, it is likely that this formed a high proportion of our 55 per cent. 'failures' who showed a good immediate response, and who subsequently

relapsed. Our psychopathic and obsessional groups showed the greatest resistance to treatment.

CONCLUSIONS

In general, there appears to be a place for E.C.T. in the treatment of the neuroses, and it seems to have a lasting effect upon a proportion of cases. It shows little specificity upon the various diagnoses, although its effect is probably mainly upon the depressive components. In practice, however, it promotes rapid alleviation and sustained improvement in a variety of non-psychotic mental disorders. Psychopathic and obsessional personalities have the poorest prognosis, but the long duration of symptoms before treatment, or the presence of marked constitutional factors, does not necessarily preclude a lasting response.

SUMMARY

The results of a follow-up survey of 77 psychoneurotic patients two to four years after treatment by electro-convulsive therapy at the neurosis centre of a general hospital are discussed, and the sustained effect and prognostic implications are assessed.

Approximately 70 per cent. of the patients are shown to have remained well; 60 per cent. of these had previously had mental symptoms of more than twelve months' duration.

Twenty per cent. of the recovered patients showed a delayed response and, as 95 per cent. of the 'failure' group were treated as inpatients, factors other than the effect of E.C.T. do not appear to have influenced the results.

Psychopathic and obsessional conditions showed the greatest resistance to treatment, but otherwise there was little difference in the effect upon the different diagnoses.

I wish to thank Dr. M. Jeffrey, consultant psychiatrist to the City General Hospital, Sheffield, for his help and facilities in the preparation of this article.

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THE OBSTETRIC EMERGENCY SERVICE

'THE FLYING SQUAD'

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THE coming-of-age of the Newcastle 'flying squad', which answered its first call on October 15, 1935, provides an opportunity for reviewing the development of the obstetric emergency service and its contributions to obstetrics. At a reception, given by the board of governors of the United Newcastle upon Tyne hospitals on February 21, it was reported that the Newcastle flying squad has responded to no less than 1,377 urgent calls. From its inception the number of calls annually increased steadily until 1939, when there were 48. There was then a slight decrease during the war years, but during the last ten years there has been a rapid increase until, in 1955, a peak of 146 calls was reached. At the coming-of-age celebrations tribute was paid to the pioneer work of Emeritus-Professor Farquhar Murray who was largely responsible for the inauguration of the flying squad.

ORIGIN AND DEVELOPMENT

It was realized in 1935 that, whilst some fatalities arose from failure to refer complicated cases to hospital, a certain number of women lost their lives as the result of their transportation. This was especially true of patients with the third-stage complications of hæmorrhage, retained placenta and shock, and it was to this group that the Service was primarily directed.

'Flying squads' are now based on no less than 172 maternity hospitals or units in England and Wales. During the last three months reviewed by the Ministry of Health (April 1 to June 30, 1956) these squads were called on 713 occasions. This implies over 2,800 calls per annum, or, expressed in another way, to 10 of every thousand domiciliary deliveries. Although third-stage complications continue to comprise some 75 to 80 per cent. of the calls, it is pleasing to note that other important uses of the service are steadily unfolding. Abortion, antepartum hæmorrhage, eclampsia, prolonged labour, undiagnosed malpresentations, multiple pregnancies, prolapse of the cord and acute inversion of the uterus are recent examples. Whilst full use of the service is to be encouraged, few obstetricians will deny that more careful selection of patients for domiciliary delivery would effect a material reduction in the strain on the personnel of the squads. Twins, grandmultiparæ, and women with a previous history of third-stage complications should not be

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booked for home confinement, for these cases make a considerable contribution to the avoidable causes of maternal death.

PERSONNEL

It is felt that the practitioner and his patient are entitled to the services of an experienced obstetrician, and this has always been the practice in Newcastle. In general it is being adopted by other squads throughout the country. By the same token we expect the practitioner to be present and to remain throughout the emergency. More recently a consultant anaesthetist has been included, and his assistance has proved invaluable. Originally the District Sister was a member of the team, but since the virtual disappearance of the 'Extern Maternity', one or other of the senior sisters in the antenatal department has been responsible for the maintenance of the equipment and invariably accompanies the squad. Her intimate knowledge of the equipment and wide experience in converting the most unpromising environment into an adequate labour room are of great value to the service.

TRANSPORT AND EQUIPMENT

Owing to the considerable distances to be covered (up to 60 miles) by the Newcastle squad, it has always proved more expeditious for the consultants to collect the Sister and the equipment at the hospital. To avoid possible delay, the anaesthetist travels in his own car. This arrangement works well, as all the consultants live within a short distance of the hospital, and it is extremely rare for the patient to be moved to hospital. The equipment is comprehensive and quite adequate to carry out all treatment—even Cæsarean section, but this has only been performed in exceptionally urgent circumstances where the squad was called to a small remote maternity unit. A similar plan has been adopted by about half of the squads throughout the country, but many other types of transport prove more convenient in certain areas, as, for instance, a hospital car, staff car, an ambulance, or a taxi. Squads operating in very restricted areas advocate simple resuscitation and rapid transfer to hospital by ambulance, but we have never regarded this as the proper role for such a service.

ORGANIZATION

In-coming telephone calls are switched direct to the labour room, where a senior sister is always available. The words 'flying squad' secure priority. Sister then informs the antenatal Sister on duty and calls the obstetrician and the anaesthetist. Great care is taken to record accurately the name and full address of the patient, the nature of the emergency, the Rh factor, and the blood group of the patient. The caller is further requested to station at an agreed point near the house a guide, equipped during darkness with a white towel or a large handkerchief for identification. This internal organization is vital to speedy service, and every effort should be made to perfect it by the cooperation of telephone operator, porter, resident doctors and

Sisters. Direct line from exchange to labour room has been suggested. The Winchester group has adopted a system of squared maps with reference numbers by which the practitioner can arrange the precise point for the guide to meet the squad.

SUBSIDIARY EMERGENCY EQUIPMENT

Although the country is reasonably well served by obstetric emergency services, long distances, resulting in inevitable delays, have to be covered in some regions. The number of squads might be increased, but difficulties of competent staffing must be remembered. Consequently the alternative suggestion of emergency equipment decentralized to doctors, district midwives, cottage hospitals or maternity homes has been made—and actually implemented in the Winchester group. This will provide for transfusion while the 'flying squad' is en route. To distribute Group O Rh-negative blood with such equipment would be wasteful, and the view of our blood transfusion service is that plasma substitutes predispose to dangerous afibrinogenæmia. We have therefore been advised to revert to 'small pool' plasma. Ergometrine, 0.5 mg., should be given intravenously, and methyl-amphetamine may be administered in some cases. The shocked patient should be kept warm but not overheated, and given only minimal sips of fluid in view of the impending anæsthesia. On no account should manual removal of the placenta be attempted until shock has been combated—and the grave danger of transporting a patient to hospital with the placenta *in utero*, even in the absence of bleeding, must be fully appreciated.

THE IMPORTANCE OF THE SERVICE

With the tremendous reduction in puerperal sepsis, the commonest causes of maternal mortality and morbidity are the 'toxæmias' and the 'hæmorrhages'. Improved methods and routine of antenatal care with more careful selection of cases for hospital can still effect further reductions. Early diagnosis and treatment of anæmia, the early detection of pre-eclampsia and hypertension, fuller investigation of the 'high head' in relation to placenta prævia before bleeding, immediate hospitalization (without internal examination) of every case of bleeding, however slight—all these will make their contribution. So long as domiciliary delivery continues, however, there will be need for an efficient 'flying squad' service. As the midwife alone attends many of these patients, she must be permitted to summon the service herself in extreme emergency when she is unable to obtain immediate help from the patient's practitioner.

In order that full advantage may be taken of the service, executive councils and medical officers of health should circulate to practitioners and domiciliary midwives, at regular intervals, information on the location and the method of summoning of 'flying squads' in their areas.

PROBLEMS IN THE HOME NURSING AND CARE OF ELDERLY PEOPLE TODAY

By Miss E. J. MERRY, S.R.N., S.C.M.

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Dr. Kitching's article in the February issue of *The Practitioner* (p. 234) brings out afresh the increasing problem of elderly people. He talks of the 'disgraceful neglect of the aged sick' and the solution he puts forward is for a new group of women to attend them, who would be part-time 'district assistant nurses'. The leading article in the same journal (p. 143) comments that it is becoming increasingly difficult to be ill at home simply because there is no-one to nurse the patient in his/her own home. This statement may be intended to mean that there are nowadays few relatives at home, or that there are insufficient district nurses.

DISTRICT NURSES

District nurses are of course employed by every local health authority in Great Britain; in fact the number employed is greater than ever before, and the Report of the Ministry of Health (Part I), states that at December 31, 1955, in England and Wales, 9,884 were so employed, compared with 9,642 in 1954. The majority of the nurses are State registered, both Queen's and non-Queen's district nurses, but some (probably 10 per cent. of the total) are State-enrolled assistant nurses. They nurse patients of all ages, including a large number of the elderly sick patients who are under the care of a doctor and are in need of special nursing treatment or of general care, often visiting those who are very ill once or twice daily.

The Ministry of Health Report (Part I) for 1955 also states that over 50 per cent. of the district nurses' visits were paid to people over 65 years of age. Such visits were to give injections and for dressings, general care, rehabilitation and supervision of patients' physical and mental well-being and whatever attention is ordered or needed during visits of an hour or less which district nurses give. Each district nurse probably makes 10 to 15 visits daily, and it is unlikely that the 9000 nurses could do more than they are now doing.

It seems that in areas where recruitment is good there is no shortage of district nurses and all calls which come from the general practitioner, the hospital or the health department can be met by the nurse. In well-served areas, where there is also an adequate supply of home helps as well as help from members of voluntary organizations—British Red Cross Society, St. John Ambulance Brigade, Women's Voluntary Services, National Old

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People's Welfare Committees—for providing nursing aids, invalid meals, night sitters-up, laundry services, no such neglect of elderly patients appears to exist. In urban areas with adequate services, there is usually one district nurse undertaking general nursing duties to every 5000 population, and in well-served rural areas, where the district nurse undertakes general nursing duties, and the small amount of domiciliary midwifery—say 14 to 20 cases per annum—there is one district nurse-midwife to every 2000 to 3000 population. It would seem that all patients living in these areas should be adequately nursed. There are, however, badly served areas which have too few nurses appointed, and if sufficient State-registered or State-enrolled assistant nurses are not provided, or allowed for in the agreed establishment, then it is surely the responsibility of the local health authorities to agree to adequate establishments and by all possible means to endeavour to obtain staff.

'DISTRICT ASSISTANT NURSES'

Dr. Kitching, however, appeals for a body of 'district assistant nurses' with duties which are not at present possible, and some which seem inappropriate, for district nurses to undertake. For elderly patients, he wants women who will sleep in the patient's home in emergencies, or sit up all night, or attend at a certain time each day so that patients can be washed and dressed punctually. These women would undertake those services and kindnesses which would be of great comfort and of curative value to patients, and when required to do so, they should be able to perform last offices. He suggests that such helpers would need very little training.

All district nurses will share Dr. Kitching's concern to provide such a useful addition to the services already available, which would undoubtedly be of great help to patients they are attending, and to many others who are not referred to them by doctors because there is no actual nursing treatment required. Such service would be a boon to general practitioners and would enable them to keep their patients in their own homes. It would also allow many individuals the blessing of remaining at home which the large majority long for, even in terminal illness.

It is likely that it would cost the State less to have a patient nursed in his/her own home, attended by the visiting district nurse, with this additional helper, part- or even full-time, than it would cost to maintain him or her in hospital at a cost of £12 to £15 a week.

But is there such a new band of women available to become 'district assistant nurses' working either full- or part-time? Conscription of women to undertake nursing is beyond serious consideration for work, particularly among the elderly, which demands a degree of compassion and a sincere desire to care for others. It seems to me extremely doubtful that such personnel can be found, as most women are already gainfully employed in full- or part-time jobs in other fields such as in factories, shops, and offices, as

well as in part-time nursing. It would seem that such womanpower does not exist, and the only solutions seem to be to widen the duties of home helps and to use more extensively the services of the nursing aids of the St. John Ambulance Brigade and of the British Red Cross Society.

ASSISTANTS TO DISTRICT NURSES

Home helps undertake all types of domestic work and do not normally undertake any nursing or the duties Dr. Kitching pleads for, such as last offices, sleeping in the house and other small kindnesses which a near relative would do. There would seem no reason, however, if they are the right type of individuals, why the duties of home helps should not be widened, especially if they worked as assistants to district nurses, who could teach them such duties as last offices. An increase in their numbers to help district nurses more than they do at present may be necessary. (The Ministry of Health Report (Part I) for 1955 states that 153,439 old people received services from home helps in 1955, compared with 134,571 old people in 1954.)

Voluntary nursing aids of the Red Cross and St. John organizations do give considerable help to district nurses in some areas, chiefly on Sundays and in their own spare time. If their use were encouraged, it is likely that they could be extensively used for the various services which Dr. Kitching mentions by actually assisting district nurses in simple nursing duties, and undertaking last offices for which they have had training. Although members of voluntary organizations, they are allowed to accept financial help in regard to meals and other expenses, and, for example, can receive 10s. 6d. a night when sitting-up with a patient. If not wearing uniform, they are permitted to accept an appropriate salary as helpers, which may be similar to the recognized scales for home helps.

From every angle, it seems desirable that elderly people should, so far as possible, be allowed to remain at home when they become sick or enfeebled, but there will still be a proportion of patients for whom a hospital bed is the only humanitarian solution. District nurses know of many such patients for whom no beds can be found and they do their best to attend them twice, and occasionally three times a day, but they give harrowing accounts of tragic cases they have nursed: aged and bedsores, gangrenous diabetics, blind persons, hemiplegics who fall out of bed, neglected recluses in dirty homes, and, most sad of all, lonely ill people whose relatives do not visit them.

Recently a Bill was introduced in Parliament by Mr. McLeavy, the Member for Bradford East, which seeks to coordinate the voluntary and public services for the welfare of old people. It will empower local authorities to make schemes to provide old people with meals, recreational and other services. At present they are only able to make grants to voluntary organizations in certain areas and the scope of some voluntary bodies is very limited.

In the House of Lords recently, Lord Amulree called attention to the case of old people, of whom a substantial minority are on the border between health and sickness, neither fit enough to look after themselves, nor yet sick enough to need hospital care. In the ensuing discussion, the Earl of Home thought that the root of the trouble was the lack of personnel to look after these old people in their own homes. He asked for better cooperation between hospital and welfare authorities and said that no Government or Act of Parliament could compel cooperation but, if common sense were applied, great improvements could be made. Lord Cottesloe said in the same debate that what was needed was not such a tidy theoretical solution, but a real understanding and knowledge of the problems and needs of individual old people.

District nurses realize that often the chief cause of unhappiness in the elderly is loneliness, and the feeling that their usefulness has gone and no-one wants their help. Relatives, friends or welfare schemes could do a great deal more to overcome this by providing some useful occupations which they could manage to undertake.

The wide concern expressed by politicians, doctors and district nurses shows that this neglect of old people is a very real problem in certain parts of the country and is likely to increase now that people live longer. It is sad to think that the wonders of medical science in prolonging life by ten to fifteen years may not always prove to be a boon.

FAMILY RESPONSIBILITY

It is saddest of all to think that the family's responsibility to care for the weaker members, the grandparents, the lonely aunt and even the parents, has almost disappeared. Some of our oriental non-Christian peoples put us to shame over this. Can it be that the National Health Service and all the provisions made by the Welfare State are largely responsible for bringing about this state of affairs? It seems that daughters and young wives would rather go out to work and earn, whether or not they really need the money, than stay in the home and undertake the much harder task of looking after those who need their tender care: their young children and their old people. Could any publicity campaign or religious revival ever recover this sense of family responsibility? If it could, it would relieve many problems of physical and especially of mental suffering, because all the nursing and care given by nurses and their auxiliary helpers to elderly people in their own homes, can never really give them the comfort and security that come from knowing that they are wanted and cherished by their own people.

GENERAL PRACTITIONERS' FORUM

PRIMARY TUBERCULOSIS OF THE INTESTINE

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PRIMARY ileo-cæcal tuberculosis in adults is a very rare condition. Crohn and Jarvis (1940) found eight cases in 4,800 necropsies at Mount Sinai Hospital between 1926 and 1938, whilst Wolfson (1938) met only three cases in 9,100 necropsies between 1925 and 1931. Bockus, Tumen and Kornbloom (1940), after an extensive review of the literature, reported two cases. Horn, Dockerty and Pemberton (1950), in a review of ileo-cæcal tuberculosis, emphasized the difficulty in distinguishing the condition from non-specific regional tuberculosis, whilst Butler (1953) is of the opinion that a large number of cases of so-called ileo-cæcal tuberculosis were probably Crohn's disease, as evidenced by a series of cases observed between 1937-52. Ukil (1942) analysed 1000 cases of intestinal tuberculosis and found 9 per cent. to be primary in origin.

In ileo-cæcal tuberculosis the gastro-intestinal symptoms commonly consist of abdominal pain, nausea, vomiting, anorexia, discomfort after meals, diarrhœa or constipation. Sometimes few of these symptoms may be present. In addition there may be loss of weight, fever, weakness, night sweats and psychotic disturbances. As these symptoms may simulate so many other disorders extensive investigation may be necessary to establish a diagnosis.

CASE REPORT

Mrs. S., aged 56 years, was seen by one of us (M.H.F.) on Dec. 12, 1954, when she complained of lassitude and loss of weight in the preceding four months. She had become extremely depressed. She stated that she had lost her appetite and on occasions suffered from nausea but did not vomit. She had never suffered from abdominal pain. She was constipated and the bowels only acted properly when she took purgatives. There was no history of diarrhœa or of the presence of blood or slime. There were no urinary symptoms. She had no cough. She had lived in India for about twenty years and had only returned to this country a year ago. She had never contracted any tropical disease. Apart from hysterectomy for a fibroid uterus in 1938 her previous history was uneventful.

On examination she appeared a frail middle-aged woman whose height was 5 feet 7 inches (170 cm.) and weight was 8 stone 2 pounds (52 kg.). She stated that she had weighed over 11 stone (70 kg.) in the previous September. She was afebrile and the pulse was 86 per minute. The conjunctivæ were pale. She was edentulous and the tongue was clean. The thyroid gland did not appear enlarged. There was no evidence of lymphadenopathy, and there was no œdema of the lower extremities. No abnormality was detected in the respiratory or cardiovascular systems. The blood pressure was 140/90 mm. Hg. Palpation of the abdomen and pelvic examination revealed no abnormality apart from the absence of the uterus.

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A provisional diagnosis of carcinoma of the bowel or of the stomach was considered and arrangements were made for her to be investigated in hospital.

Ten days later she was seen again at her home. Her husband stated that for about a week she had been running a temperature of 100°F . (37.8°C .) at night, the morning temperature being normal. The depression was now more severe. She was still constipated. The clinical findings were similar to those found originally.

Two days later she was removed to hospital where the following investigations were performed:—

Blood count: R.B.C. 4,200,000 per c.mm. Hæmoglobin 82 per cent. C.I. 0.97. W.B.C. 6000 per c.mm. Polymorphs 65 per cent. Lymphocytes 30 per cent. Monocytes 4 per cent. Eosinophils 1 per cent.

Erythrocyte sedimentation rate: 20 mm. in first hour.

X-ray of chest: No abnormality detected.

Barium enema: Small diverticulæ of the colon.

Barium meal: Negative.

Intravenous pyelogram: Negative.

Urine: A few pus cells. No red cells. Very faint trace of albumin. No tubercle bacilli found on culture.

Fæces: *Shigella sonnei*, *shigæ* and *flexneri*—negative.

Blood: Culture: No growth after prolonged incubation. Total protein 5.5 g. per cent.; albumin 2.7 g. per cent., globulin 2.8 g. per cent. Electrophoresis confirmed diminished albumin and showed marked emphasis of alpha globulins and a moderate increase in gamma globulins—suggestive of tissue necrosis connected with neoplasm or abscess. *B. paratyphosus B. (H)* positive to a titre 1/20. No agglutination with *B. typhosus* (H and O), *B. paratyphosus B. (O)*. Wassermann and Kahn reactions negative. Complement fixation tests for influenza A and B, psittacosis and Q fever negative at 1/4. *Strep. M.G.* agglutination negative at 1/20.]

While in hospital the temperature became remittent, the maximum being 103°F . (39.4°C .) in the evening. Penicillin, 1 mega unit twice daily for five days, had no effect on the temperature, whilst 1 gramme of streptomycin three times daily for one week did reduce the evening temperature to 100°F . (37.8°C .) She was seen by a consulting surgeon who confirmed the diagnosis of carcinoma and considered laparotomy was unjustified in view of her poor condition. After a fortnight she weighed only 6 stone 7 pounds (41 kg.). She had become progressively weaker and her hæmoglobin was 40 per cent. Acute depressive melancholia was well marked. A week before her death she developed diarrhœa and incontinence of fæces. Her condition deteriorated rapidly and she died four weeks after admission.

Post-mortem examination revealed the presence of numerous yellowish nodules in the distal two feet (60 cm.) of the small intestine. The nodules were in clusters and associated with localized thickening of the gut wall. No ulceration of the mucosa was present. The lesions were suggestive of either Crohn's disease, tuberculosis or carcinomatosis (fig 1). Sections of these nodules revealed the presence of characteristic giant cells, and tubercle bacilli were seen in one specimen. No abnormality was found in any other organs.

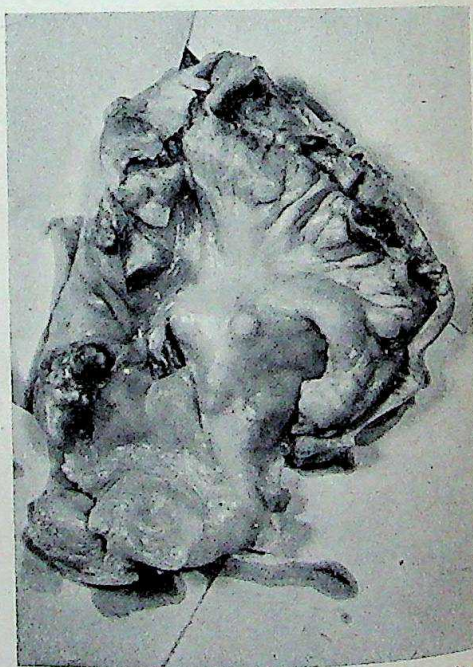


FIG. 1.—Ileo-cæcal junction showing tubercles.

DISCUSSION

It would appear that this patient must have contracted intestinal tuberculosis from drinking infected milk, probably in India. During the first few months of the illness the disease manifested itself by lassitude, anorexia, nausea, constipation, and loss of weight. Abdominal pain was never present, and diarrhoea only developed a week before death. Acute depression was a well-marked feature of the case. The toxæmia was most severe in view of the limited extent of the lesions found at post-mortem examination.

The diagnosis of carcinoma of the bowel appeared so strong that a barium enema was the first line of investigation, and the question of ileo-cæcal tuberculosis was not considered. A follow-through after a barium meal and an examination of the stools for tubercle bacilli would certainly have established a correct diagnosis. A more careful assessment of the effect of streptomycin in reducing the diurnal range in temperature might have offered a helpful clue.

SUMMARY

A case of primary ileo-cæcal tuberculosis is described, the duration of the illness being short, and accompanied by a profound toxæmia. The importance of a full x-ray investigation together with an examination of the fæces for tubercle bacilli is stressed.

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THE USE OF PHENYLBUTAZONE IN THE TREATMENT OF SUPERFICIAL THROMBOPHLEBITIS

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ACUTE superficial thrombophlebitis remains a fairly common disorder in general practice. In the past, treatment has entailed bed rest, soaks, antibiotics and local medications, usually effective but seldom bringing prompt relief and often definitely protracted. Following claims by Stein (1954, 1955), in the United States, that phenylbutazone was a more rapid and effective means of treatment, we decided to use it in selected cases in our practice.

METHOD

Recognizing the known contraindications to the use of the drug, we did not give it to any patient in whom there was any fear of cardiac decompensation, or who had a history of peptic ulceration, blood dyscrasia or drug allergy—nor in patients with hypertension or renal or hepatic damage.

No treatment apart from phenylbutazone was given, and all patients were kept ambulant except the two suffering from malignant disease who were, in any case, confined to bed before the onset of phlebitis. We decided to use an average dose—100 mg. thrice daily—and eventually found that in no case was a total dosage of more than 1.5 g. given.

We have now treated fifteen such cases in this way. Varicose veins were the etiological factor in twelve of the fifteen, malignant disease in two, and in the other case the phlebitis occurred spontaneously in clinically normal veins and was presumably idiopathic migratory thrombophlebitis—a finding in agreement with Stein's much larger series. In general practice, of course, we did not see any drug or chemically induced phlebitis due to intravenous therapy.

RESULTS

We found that treatment was remarkably successful and safe (table I). In all but one of the cases pain in the affected limb had disappeared or was considerably lessened within twenty-four hours. In three days all local redness and swelling over the inflamed area had disappeared, and any accompanying systemic upset with fever and malaise had also regressed.

Type of superficial thrombosis	No. of cases	Resolution	
		Complete	Incomplete
In varicose veins	12	12	0
In malignant disease	2	1	1
In idiopathic migratory phlebitis	1	1	0

TABLE I.—Results obtained with phenylbutazone in 15 cases of superficial thrombophlebitis.

Only in one case was recovery temporary, and that was a man who had an inoperable carcinoma of the lung and in whom the phlebitis was soon overshadowed by other disease processes.

The following are three typical case histories:—

Case No. 1.—Mr. F., age 48 years, had recurrent superficial thrombophlebitis. For 23 years he had, every second or third year, to spend up to three weeks in bed on account of thrombophlebitis of one or other leg. In 1953, when in hospital, he was attended by one of us (H.H.A.E.) following a superficial phlebitis of the left leg—the deep veins of the calf became involved and he had a pulmonary infarction. At one stage his employment was threatened as he was off work so constantly. In January 1956, he again had a superficial thrombophlebitis of the left leg. This time he was given phenylbutazone, 100 mg. thrice daily, and told to stay at work. In three days the inflammation had gone, all redness and tenderness over

the vein had disappeared and the leg was much less swollen. In seven days the leg was completely normal.

Since this episode, on several occasions the patient, an intelligent man, has been aware that a superficial thrombophlebitis was about to recur and taken 100 mg. thrice daily for two days, completely aborting the attack.

Case No. 2.—Mrs. C., age 58 years, had already been in bed for three weeks receiving local applications and the like when we first saw her. She was then put on phenylbutazone. In three days she had started to get up and walk around, all pain, redness and swelling having disappeared.

Case No. 3.—Mr. W., age 72 years, had been in bed for a month because of cachexia associated with inoperable carcinoma of the prostate, when he developed superficial thrombophlebitis of the left leg. After five days on phenylbutazone his leg looked and felt as normal as its fellow, apart from some cord-like thickening where the veins had thrombosed.

COMMENT

We believe that phenylbutazone is a valuable and efficacious drug in the treatment of superficial thrombophlebitis in general practice. As the dosage employed to obtain resolution of the inflammatory process is small, the possibility of side-effects or dangerous toxic reactions is considerably reduced and we have no complications to report.

The rapidity of resolution on this treatment represents a valuable reduction in time spent in bed and in economic loss. The avoidance of bed rest, made possible largely by rapid control of systemic upset and pain must, we believe, reduce considerably the incidence of deep vein thrombosis and the unpleasant complication of pulmonary embolism.

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A TALE OF GIN

By A GENERAL PRACTITIONER

ONE day last spring I was summoned to attend a patient of another doctor who had gone on holiday, and for whose patients I was 'on call'. The man was fairly moribund, and dying in that state of misery, pain and wretchedness which so often accompanies the terminal stages of malignant disease. I therefore prescribed for him, without hesitation, what I had so often dispensed in my previous sphere as a qualified pharmacist, namely, 'Haustus Euphoriens': morphine and cocaine in a vehicle of honey and gin.

GIN NOT A 'DRUG'

Within a matter of weeks, I was informed, as I expected, that the gin was not a 'drug', but that I had the right of appeal to our local medical com-

mittee. Just before my appeal was due to be heard the July issue of *The Practitioner* came to hand, and, to my joy and pleasure, in an excellent article by Dr. Douglas G. French, of Kidsgrove, there appeared (p. 85) the replica of my prescription. By an extraordinary coincidence that week also, I received a copy of *Clinical Excerpts*, in which my prescription was again identically repeated. Armed with these two publications, confident in the rectitude of my conscientious prescribing, confident in the full support of colleagues who, I expected, would say 'his action was right, we acknowledge the proof he has brought', confident that I would be allowed to pass the two journals round the committee, I was shocked to find that the members of the committee were interested in neither the case nor my principles, and had already decided that I was wrong, whatever sort of justification I put up.

Shocked and angered by this attitude, which was confirmed by their letter saying the medical committee had failed to support me but that I still had the right of appeal to the Minister, or at least to his referees, I appealed, explaining the case, and sending forward the two aforementioned publications.

THE SEQUEL

After some weeks, the following facts emerged. In the absence of the patient's own doctor, I was in the position of 'locum' for him, and hence I could not be charged for the gin. The patient's doctor, now faced with the staggering bill of 8s. 1d., checked his records and found that he had been treating this man, amongst others, who had never been on his list, and for whom, and for 30 years, he had never received any payment. Further, this man was to all intents and purposes a phantom for he did not even appear in the records of the executive council.

To save embarrassment all round, it was arranged that I should withdraw my appeal, and that the case should be dropped into the limbo of forgotten things.

THE POINT AT ISSUE

What still worries me, however, is this: I virtually followed out the prescription, or recommendation, of a contributor (of considerable standing) to *The Practitioner*, a periodical which I take to be recognized as an organ of good general practice. This recommendation, however, did not receive either confirmation or approbation, in the light of present-day National Health Service trends, which of course are those that we as general practitioners must recognize. I know that Dr. C. A. Clarke (*The Practitioner*, 1957, 178, 38) has subsequently given us a way of getting round this Ministerial ban on the medicinal use of gin. Such subterfuges, however, are scarcely in keeping with professional standards of conduct, and therefore I still feel that a matter of principle is at stake. By what standards are we general practitioners to be guided? Those of the medical journals we read, or those of the bureaucrats of Savile Row and St. Andrew's House?

HOW TO WRITE A MEDICAL BOOK

By M. O'DONNELL, M.B., B.CHIR.

Battersea, London, S.W.11

THIS article is designed neither for the inarticulate physician nor for the frustrated 'littérateur'. It is written to enable junior members of the profession to overcome the most serious difficulty that faces them today—how to earn some money. Personal investigation (Cope's and Vernon's 1955; Littlewood's 1956) has convinced me that one of the simpler methods of tackling this problem is to write a book, and considering them from a purely remunerative angle I have found that medical books fall into four main categories.

CLASSIFICATION

Group 'A'.—The COMMERCIAL Medical Book.

This is for the truly lazy and avaricious author. The sole qualification which places a book in this category is the inclusion of one of the following phrases in the title. (They are starred according to selling power.)

- ***** Sexual behaviour.
- *** Marital technique.
- ** Talks for young girls (or boys, or both).
- * Diseases of the female.

Group 'B'.—The MEMOIR.

Properly handled this can be a very strong seller. Titles range from 'The world was my practice' to 'Fifty years of fibroids in the Faroes'. To push sales really effectively get a photograph of one of your middle-aged uncles, preferably smoking a pipe, and stick it on the back of the dust jacket labelled 'The Author'.

Group 'C'.—The TEXTBOOK.

If you are in the position to compel students to buy this, it can be the best investment of all.

Group 'D'.—The ARTICLE.

This is mentioned merely for the sake of completeness. It earns nothing save a certain amount of kudos in somewhat rarefied circles. Titles tend to be longwinded: e.g. 'Some further considerations of the morphology of the third metatarsal in the Nicaraguan'.

THE 'FILLING'

Once the group and the title have been chosen, the immediate consideration is the 'filling'.

Group 'A'.—Here the 'filling' is quite simple. One merely paraphrases

the relevant chapters in 'Ten Teachers', Marie Stopes or *The Church Lad's Gazette*.

Group 'B'.—The 'filling' is a little more difficult. It must have what the critics call 'conflict' and what you and I call a good story. Get one of your patients to tell you one. Then pad it out with young probationers falling in love with middle-aged physicians, middle-aged physicians falling in love with young probationers and middle-aged surgeons falling in love with themselves.

The ending is very important. It must be one of two types: (a) Everything turns out all right. (b) Everything turns out all wrong. There must be no compromise between the two.

Group 'C'.—Here the 'filling' is of no importance. The only important thing is the preface and at least half of this must consist of acknowledgments. Prominent among these must be your debt to your wife. (If your home life is unhappy, substitute 'devoted secretary'.)

You must thank your senior colleagues for unsolicited advice which you never followed and I cannot overstress the importance of one long paragraph expressing eternal indebtedness to some obscure professor in Equatorial Africa 'for his inestimable kindness in lending the photograph of the Nigerian knee-cap opposite page 583'. It is essential that this eulogy should be at least three times as long as the paragraph thanking your junior colleagues who have compiled the index, assembled the statistics, collected the cases, annotated the bibliography and who have, in short, written everything in the book except the preface.

CONCLUSION

Charles Churchill (1731-64) wrote in 'The Ghost' (bk. iii, 1, 801):

'He for subscribers baits his hook,
And takes your cash; but where's the book?'

It is suggested that impoverished members of the medical profession show him precisely where it is.

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CURRENT THERAPEUTICS

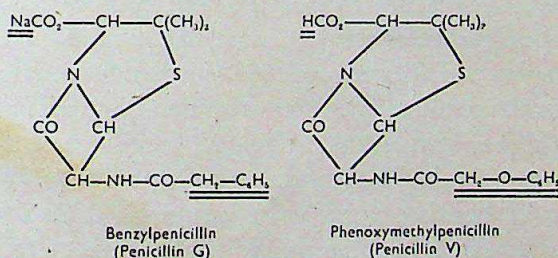
CXII.—PENICILLIN V

(PHENOXYMETHYLPENICILLIN)

By JOHN MACLEOD, M.B., F.R.C.P.ED.

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THERE have been three main stages in the evolution of the penicillins for therapeutic purposes. First there were the potassium, sodium and other salts of the organic acids produced by *Penicillium notatum*, of which the most important is benzylpenicillin (penicillin G). Then came the salts of benzylpenicillin with organic bases, such as procaine benzylpenicillin, benzathine penicillin and benethamine penicillin, the main contribution of which was to prolong the action of penicillin. Now penicillin V is available. This is a new form of penicillin which is prepared by adding N-(2-hydroxyethyl)-phenoxyacetamide to the medium in which the mould is growing. As is indicated by its official name, phenoxymethylpenicillin, penicillin V differs from penicillin G in that a phenoxymethyl group replaces the benzyl group:—



It will be seen from the structural formulæ that there is a difference of only one oxygen linkage between the two preparations, and that one is an acid and the other a salt. Benzylpenicillin is stable only in the form of a salt, whereas phenoxymethylpenicillin is stable either as an acid or a salt. It is as the free acid that the latter is at present marketed and its stability in acid media confers on it its unique properties.

Penicillin V was first prepared in the United States by Behrens and his colleagues (1948). The significance of its stability in the pH range below 5 was recognized when it was investigated some five years later in Austria by Brunner (1953) and by Brandl and Margreiter (1954). This property renders penicillin V much more resistant to inactivation by gastric juice than other oral penicillins. These workers also demonstrated that this preparation was readily absorbed from the intestinal tract when given by mouth. Since then it has been used with increasing frequency, and in 1955 it was

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claimed that in Sweden some 40 per cent., and in Austria some 30 per cent., of all penicillin prescribed was penicillin V.

There are varying quantitative differences in the action of penicillin V against the organisms used in biological assay and its measurement in units is not practicable. Dosage is therefore determined in milligrams. *By chemical assay 60 mg. of penicillin V is equivalent to 100,000 units of penicillin G.*

ABSORPTION, BLOOD CONCENTRATION AND EXCRETION

Penicillin V is unaltered by its passage through the stomach, whether taken before or after a meal. It is soluble in the alkaline contents of the proximal small intestine and is readily absorbed. The residue is inactivated by penicillinase in the lower bowel and is therefore unlikely to disturb the balance of the intestinal flora. In assessing the blood levels, comparison with penicillin G, rather than with benzathine penicillin, is desirable, as initial claims that the latter antibiotic is better absorbed from the gut and gives higher blood levels than the former have not been substantiated by later workers such as Bayne *et al.* (1953) and Fairbrother and Daber (1954). The Austrian claims that penicillin V produces blood levels considerably higher and more prolonged than those following an equivalent dose of penicillin G have now been confirmed by many other workers, including Wright *et al.* (1955), Martin *et al.* (1955), and Rinsler and Cunliffe (1956). The last of these showed that the levels attained after 120 mg. of penicillin V were about double those following an equivalent dose of penicillin G, and compared favourably with the blood levels following 100,000 units of penicillin G given by intramuscular injection. It has also been established that penicillin V gives much higher and more prolonged blood levels than benzathine penicillin given by mouth (Henry *et al.*, 1957).

Difficulties from malabsorption from the small intestine, such as have occurred with penicillin G in some individuals, have not so far been reported. Penicillin V is rather more slowly absorbed and takes slightly longer to produce its highest blood level than penicillin G, but any disadvantage of this delay is outweighed by the much higher and more prolonged levels which are reached. Detectable blood levels are still present six hours after the administration of 120 mg. of penicillin V, whilst none is detectable at this time after an equivalent dose of penicillin G. In children adequate blood levels may reasonably be expected up to three hours and possibly up to five hours after 120 mg. of penicillin V (Holborrow, Bywaters and Johnson, 1956). These authors also point out that higher blood levels are obtained when this preparation is given half an hour after food than if it is taken one hour before food. Others, such as Jones and Finland (1955), have demonstrated a similar effect of meals on absorption. Very much higher levels can be produced by the concurrent administration of probenecid which inhibits the excretion of penicillin V by the renal tubules. The levels are three to four times greater than those produced by equivalent doses of penicillin G and probenecid (Cox *et al.*, 1957).

Penicillin V is widely diffused throughout the body. It passes into pleural and ascitic fluids but not into the cerebrospinal fluid. It is excreted in the bile and in the urine. About a quarter of the dose given can be recovered from the urine. Whilst this is about twice as much as in the case of penicillin G, and points to the inferior stability of the latter, it also indicates that absorption of penicillin V is by no means complete. This 25 per cent. excretion of the phenoxymethyl derivative compares unfavourably with the 60 per cent. which is excreted in the urine when penicillin is administered by injection.

ANTIBACTERIAL ACTIVITY

For all practical purposes the spectra of penicillins V and G are the same. There are some minor differences: for example staphylococci tend to be more sensitive to penicillin V and some streptococci are more sensitive to penicillin G.

PREPARATIONS, DOSAGE AND COST

Penicillin V is available in tablets containing 60 mg. and in capsules containing 60 mg., 125 mg., or 250 mg. Palatable suspensions are dispensed for administering the antibiotic to children. An average dose for an adult suffering from an infection of moderate severity due to an organism sensitive to penicillin is of the order of 120 mg. four-hourly, the last two doses being administered together before retiring. For children half the adult dose and for infants one-quarter of the adult dose are prescribed. The antibiotic should preferably be given after food in order to take advantage of the higher blood levels that result. If it is desirable to avoid any delay in obtaining an effective blood level an initial injection of 100,000 units of penicillin G is indicated. If very high blood levels are required from oral medication, penicillin V may be given in doses of 240 mg. or more, or combined with probenecid (0.5 g. six-hourly or twelve-hourly).

The current retail price of penicillin V in doses of 120 mg. four-hourly for five days is about twenty shillings. In comparison, 600,000 units of procaine benzylpenicillin once daily for this period would cost about half this price, but other expenses, difficult to compute, are incurred when any preparation is given by injection. The price of penicillin V compares increasingly favourably with penicillin G given intramuscularly in proportion to the number of injections given. It must be remembered, however, that sulphadimidine is still less expensive.

CLINICAL APPLICATIONS

Clinical trials conducted in Europe and America have produced very encouraging results in a wide variety of infections due to penicillin-sensitive organisms. Streptococcal infections (tonsillitis, pharyngitis, bronchopneumonia and erysipelas), pneumococcal infections (lobar pneumonia) staphylococcal infections (carbuncles and osteomyelitis) and spirochætal infections (Vincent's angina) have all been treated successfully. Uniformly good results have been reported from Great Britain in the treatment of

a miscellaneous group of conditions of this type in general practice by Bowerbank (1955), Dove (1955) and Jolles (1956); in hospital practice in the United States by Martin *et al.* (1955) and by Wood *et al.* (1956); and in Europe, both in and out of hospital, by Hausmann and Zischinsky (1953) and by Schindelmaisser (1954). In dental practice, conditions such as apical abscesses and osteitis have been treated successfully by Herrmann (1955).

More detailed studies of the effect of penicillin V in specific conditions are now becoming available. Patients suffering from lobar *pneumonia* or other respiratory infections, including broncho-pneumonia, were treated either with penicillin G by intramuscular injection (1 mega to 1.2 mega units daily), or with penicillin V (60 to 120 mg. four-hourly for at least five days), at St. Stephen's Hospital, London, by Hart and his colleagues (1956). The selection of the method of treatment was made at random, two comparable groups of 12 cases were studied and the clinical response was roughly identical. The patients preferred the oral treatment. The authors suggested that penicillin V would prove to be a practical alternative to parenteral penicillin which should be particularly useful in busy general practice. At the 1956 Symposium on Antibiotics at Washington, McWhorter and his colleagues from Cincinnati found that penicillin V, in doses varying from 375 mg. every four hours to 300 mg. every six hours, was effective in the treatment of patients moderately or severely ill with lobar pneumonia. On the other hand, the efficacy of sulphadimidine in the treatment of this condition must not be forgotten.

Breese and Disney (1956) have treated 110 children in Rochester, N.Y., suffering from β -*haemolytic streptococcal infections*. The clinical response was excellent and cultures rapidly became negative. They claimed an overall 'cure' of approximately 90 per cent.

Encouraging results have been obtained in acute *gonorrhœal urethritis* by Marmell and Prigot (1956) and by Love and Weir (1956).

Subacute bacterial endocarditis should provide a critical test of the therapeutic efficiency of penicillin V. Results have been claimed which compare favourably with those achieved by the parenteral administration of penicillin G. Quin and his colleagues (1956) treated four patients with subacute bacterial endocarditis. Two of these with a *Streptococcus viridans* infection were treated with 7,200 mg. daily for six weeks and showed a satisfactory clinical and bacteriological response. A third case was due to an unusual organism, *Neisseria sicca*, and was treated successfully with penicillin V orally and streptomycin intramuscularly. In the fourth patient remission could not be maintained but the infection proved to be due to a penicillin-resistant staphylococcus. In one case success has been claimed with two weeks' treatment when penicillin V was supplemented with streptomycin (Martin *et al.*, 1956). At the Symposium on Antibiotics in 1956, Cox and his colleagues reported success in the treatment of 13 out of 14 cases of the disease using 'a high oral dose regime of penicillin V'.

Much further careful study will obviously be necessary before it is possible

to say whether penicillin V given orally will have a place in the treatment of subacute bacterial endocarditis, but the encouraging results already obtained are an indication of its potency in a severe infection.

It has thus been established that penicillin V in doses of 240 mg. four-hourly is effective in patients seriously ill from infections due to penicillin-sensitive organisms, but the use of penicillin V in these circumstances is still at a stage when there must be a most critical appraisal of the results obtained. It will often be necessary to supplement penicillin V with penicillin G by intramuscular injection, at the initiation of treatment in urgent cases, or by local injection, in infections of the joints or of the pleural cavity.

ADVERSE EFFECTS

Penicillin V has been administered for long periods in very large doses to animals and to humans without adverse effects. Glassman and his colleagues (1956) studied tissue sections from animals in these circumstances and found no evidence of any specific damage in organs such as the liver or in the bone marrow. Diarrhoea may be troublesome but is rare and seldom interferes with treatment. It is presumably the result of an alteration in the intestinal flora. Sore tongue and vomiting have been reported but not as more than temporary inconveniences.

Sensitivity phenomena ranging from mild erythema to frank 'serum sickness' occur infrequently. In the report on new and non-official remedies by the American Council on Pharmacy and Chemistry (1956) it is stated that in rare instances penicillin V may cause acute anaphylactic shock, although this is less likely than after the parenteral administration of other penicillin preparations. No details of specific instances are given in this report and I have not come across any account in the literature of such a happening, although severe anaphylactic reactions have been described following the use of other oral penicillins. I have had the opportunity of discussing this problem with many practitioners who have used penicillin V extensively and none has encountered any serious difficulty from sensitivity phenomena. Clearly, however, penicillin V must be used with caution in patients with a history of asthma or allergy.

A history of sensitivity to penicillin G does not necessarily mean that the patient will be sensitive to penicillin V. This absence of cross-sensitivity in many cases appreciably adds to the usefulness of penicillin V in view of the increasingly high incidence of sensitivity to penicillin G. Another advantage of the former is that doctors and nurses do not have to handle the preparation and therefore run little risk of becoming sensitized in the course of their work.

CONCLUSIONS

Penicillin V is the penicillin of choice for oral use.

Penicillin V given by mouth is as effective as penicillin G given intramuscularly in the treatment of pneumococcal and hæmolytic streptococcal infections and may be more effective in the treatment of staphylococcal

infections. In these circumstances it is to be preferred to parenteral penicillin if the patient is reliable, has no difficulty in swallowing and is not vomiting.

A dosage of 120 mg. four-hourly gives blood levels which compare favourably with those produced by 100,000 units of penicillin G intramuscularly and is adequate for adults suffering from infections of moderate severity. It is preferable to give the antibiotic after meals and the last two doses may be administered together on retiring. For severe infections 240 mg. or more four-hourly will be required, and in urgent cases it is desirable to supplement treatment at the outset with penicillin G by intramuscular injection.

Further carefully supervised studies will be required to ascertain the efficacy of penicillin V in the treatment of gonorrhœa and subacute bacterial endocarditis and in the prophylaxis of streptococcal infections.

Penicillin V is very well tolerated and unlikely to cause any harmful effects other than slight diarrhœa or an occasional sensitivity reaction. Patients who are sensitive to penicillin G are not necessarily so to penicillin V, but in these circumstances the latter must be given with caution.

Until more experience of the effects of penicillin V is available it is essential that physicians should continue to be highly critical of its therapeutic efficiency and to be on the alert for any adverse effects.

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EQUIPPING THE SURGERY

IV.—THE OPHTHALMOSCOPE

By A. McKIE REID M.C., T.D., F.R.C.S.

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'But, soft, what light through yonder window breaks?'

Romeo and Juliet.

WHEN, in 1851, Helmholtz discovered the ophthalmoscope von Graefe cried 'Helmholtz hat uns eine neue Welt erschlossen'. The credit for being the first man to see the living human fundus should perhaps be given to Charles Babbage, an English mathematician who, in 1847, projected a beam of light into the subject's eye from a mirror through a hole in the centre of which he observed the beam reflected from the retina of the subject. This idea, however, was not published until seven years later.

HOW IT WAS DEVELOPED

The principle having been established, improvements and modifications followed rapidly. A concave mirror was used as a reflector increasing the illumination; a case carrying a battery of different-powered lenses was fitted behind the aperture. The *indirect* method was evolved and compact easily handled instruments were designed by various makers. Illumination of the reflecting ophthalmoscope in early days was by oil-lamp, then by naked gas-flame and later the incandescent mantle, followed by the carbon-filament electric bulb. The introduction of small torch-bulbs and dry-batteries led the way for the self-luminous or *electric* ophthalmoscope, the forerunner of the stream-lined instruments we use today in which the current is supplied by a battery in the handle or, through a transformer, from the mains supply. Juler introduced a prototype into England in 1886, but the electric ophthalmoscope only came into general use in this country between the turn of the century and the 1914-18 War, and in continental clinics the non-luminous ophthalmoscope was used in teaching clinics right into the twenties.

HOW IT IS USED

There are two main methods of ophthalmoscopy: the *indirect* method and the *direct* method, each with its own technique and relative advantages.

(a) *Indirect method*.—The apparatus is simple. The source of illumination, a frosted filament-bulb, is placed just above the patient's head. The examiner is seated at arm's length from the patient and holds in front of his eye a concave mirror with a hole in the centre (fig. 1). A beam of light is directed through the patient's pupil: the beam is reflected by the retina and is

brought to a focus by a 13-diopter lens held in the examiner's left hand in front of the patient's eye. The focused image of the retina is a real, inverted image, magnified about five diameters. In order to see the disc the beam must be directed through the patient's pupil in the direction of the centre of the patient's head, the patient looking straight ahead. The eye of the

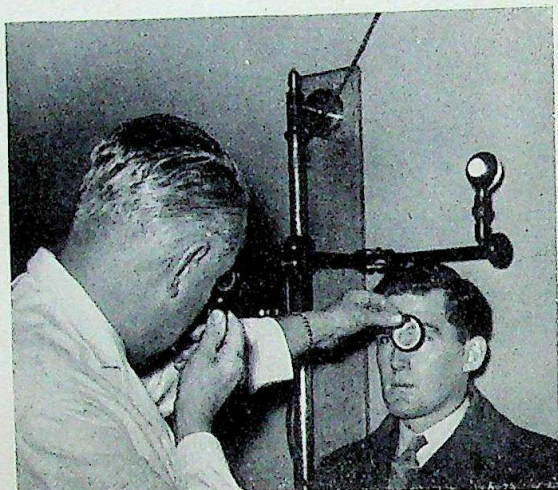


FIG. 1.—Indirect ophthalmoscopy.

ophthalmoscope, as opposed to the older *reflecting* model, is now favoured in using the direct method. The hood of the ophthalmoscope is supported by the examiner's eyebrow and the ophthalmoscope is brought directly in front of the patient's eye and as close as possible, so that the examiner's and patient's eyebrows are almost brushing (fig. 2). The examiner should use his right eye for the patient's right eye and vice versa. When the examiner



FIG. 2.—Direct ophthalmoscopy.

examiner, the convex lens and the pupil of the patient must be in the same horizontal plane. The examiner, by moving his head and the lens in various directions, can examine the region surrounding the disc. The peripheral region is examined by directing the patient to move his eye, not his head, up-and-in, directly up, up-and-out and so on, until the fundus is traversed in every direction.

(b) *Direct method*.—The electric or self-luminous electric or self-luminous ophthalmoscope, as opposed to the older *reflecting* model, is now favoured in using the direct method. The hood of the ophthalmoscope is supported by the examiner's eyebrow and the ophthalmoscope is brought directly in front of the patient's eye and as close as possible, so that the examiner's and patient's eyebrows are almost brushing (fig. 2). The examiner should use his right eye for the patient's right eye and vice versa. When the examiner and patient are both emmetropic the examiner looks through the sight-hole and obtains a clear view of the fundus without an intervening lens. When either patient or observer is ametropic a suitable lens is rotated in front of the sight-hole. The image is erect, is virtual, and the magnification is about 15 diameters.

A pattern of instrument which is popular is the Lister-Morton self-luminous ophthalmoscope (fig. 3). It is a sturdy instrument

which will withstand a fall and although it is fairly costly (about £20) it will last a life-time. Another deservedly popular model is the 'wide-angle' ophthalmoscope. Other instruments, with trimmings such as slits and filters, are more vulnerable but should not be overlooked in choosing an instrument.

The preliminary examination of the fundus is best carried out by the indirect method for, although the magnification is less, the field in any given direction is wider and it can be used independent of errors of refraction in the patient's eye. The direct method, with its higher magnification, facilitates

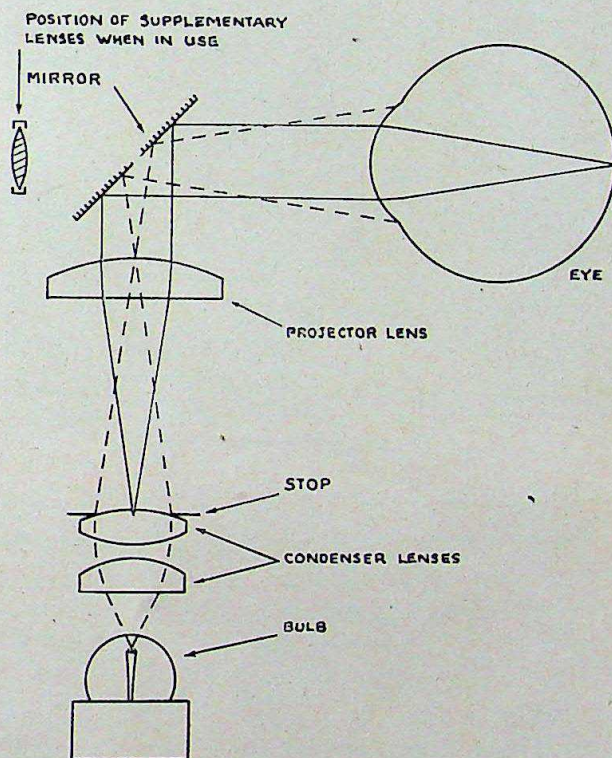
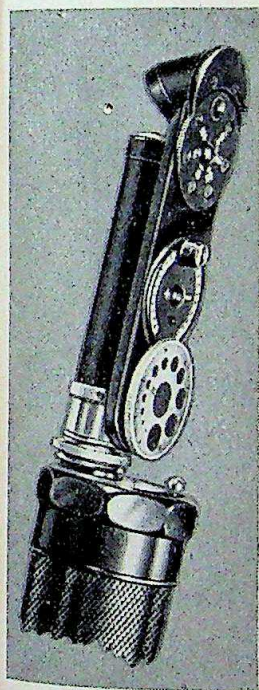


FIG. 3.—The Lister-Morton self-luminous ophthalmoscope.

a minute examination of any detail in the fundus to which attention has been drawn by the indirect method.

MODIFICATIONS OF OPHTHALMOSCOPY

The fundus may be examined by *red-free light*, inserting a green filter in the sight-hole of the ophthalmoscope.

The vessels appear black against the yellowish-green background and the actual nerve-fibres of the retina can be seen. The slit-lamp and corneal-microscope can be adapted to permit of *binocular ophthalmoscopy*. The fundus can be demonstrated to students by the *demonstration ophthalmoscope* (fig. 4) in which branch viewing-tubes are spread out, octopus-like, from the main viewing-tube, so that the demonstrator and as many as eight students can view the fundus simultaneously. Cameras have been designed to *photograph* the fundus and clinical artists have been trained to *paint* fundus pictures.

It cannot, however, be too strongly urged that the ophthalmologist or other clinician who is using an ophthalmoscope should train himself to make a sketch-drawing of every unusual fundus. Even a rough sketch showing the disc and the blood vessels with anomalous features marked in their respective positions is often

more valuable than many lines of written description.

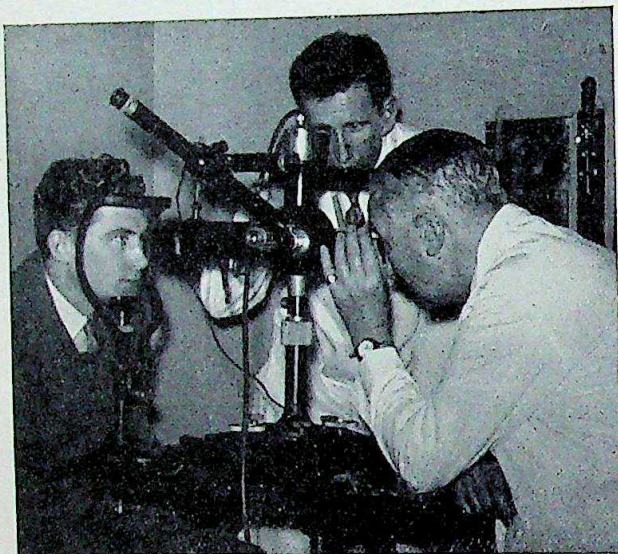


FIG. 4.—Demonstration ophthalmoscope.

WHAT TO LOOK FOR
The ophthalmoscope can be used as a torch-beam to illuminate the anterior segment of the eye and, in conjunction with a corneal-loupe, the cornea can be examined minutely. By oblique or by direct illumination the iris and lens can be examined; and the vitreous can be examined directly with appropriate lenses rotated in front of the sight-hole of the direct ophthalmoscope to bring opacities in that medium into focus. The ophthalmoscope can also be used to estimate errors of refraction. The unique and *essential* purpose of ophthalmoscopy, however, is to examine the living fundus or background of the eye (fig. 5). The fundus comprises that part of the retina which can be seen by the ophthalmoscope, with the optic disc, the macula, the blood vessels and anomalies or abnormalities of any or all of these. There is no standard-pattern fundus and its appearance, even in healthy subjects, is so protean that it is only by examining every known normal fundus that variations can accurately be known as pathological.

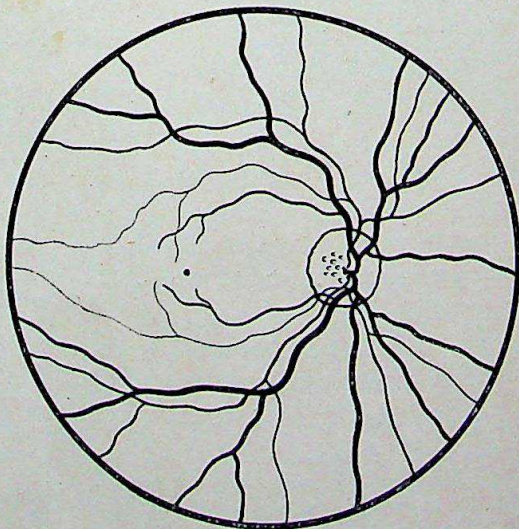


FIG. 5.—The normal fundus. Note: In making a rough sketch on a case sheet only the main four vessels need be drawn.

In examining the fundus a habitual systematic order is essential to avoid missing anything of importance. A suggested order is: the disc, the macula, the blood vessels and the retinal background.

THE OPTIC DISC

The optic disc is as individually characteristic as a finger-print and its pattern is probably only repeated in an identical twin. Indeed, the optic discs and retinal vascular distribution were criteria in settling a dispute in Switzerland to decide which two of three boys were, in fact, identical twins.

The inspection of a disc calls for a definite plan. A 'C' mnemonic is sometimes helpful:—

Colour faintly pink, pale or atrophic; *circumference*—clear-cut, blurred or absent disc-margin; *crescents* in myopia; *contour*—swelling or cupping; *circulation*—the state and distribution of the vessels; *cribrosa*, lamina, whether abnormally obvious or not visible; and *curiosities* or abnormalities such as neuroglia, pigment, hæmorrhage and so on.

Colour.—The normal disc is light-pink in colour and is relatively paler in the temporal half, which is free from vessels, than in the nasal segment in which the vessels are closely aggregated.

In *optic atrophy* the colour of the disc is altered. There are different ways of classifying optic atrophy but the following is suggested as comprehensive.

(a) *Primary*, or simple, where there has been no antecedent swelling of the nerve-head and no obvious disease of the retina causing degeneration of the ganglion walls.

The cause may be direct trauma to the nerve as in a fracture involving the apex of the orbit; demyelinating diseases; toxins such as lead, quinine; neurosyphilis (in 10 per cent. of cases in which optic atrophy is found); vascular disease such as temporal arteritis; neoplasms pressing directly upon the nerve as in the Foster-Kennedy syndrome.

The characteristic change is pallor—white, grey or bluish. The disc-margin is clear-cut, the lamina cribrosa is easily seen and there is an absence of small vessels on the surface of the disc. The disc resembles a white moon in a blood-red sky.

(b) *Secondary*.—This occurs when the ganglion-cell layer of the retina has been damaged by observable pathological processes in choroid or retina such as choroido-retinitis, primary pigmentary degeneration (retinitis pigmentosa) and so on. The appearance of the actual disc may be the same as in primary optic atrophy but the general fundus picture shows the cause to which the atrophy is the secondary effect.

(c) *Consecutive*.—This occurs when the disc has been previously choked by papilloedema which has subsided. The exudate undergoes organization and obscures the pattern of the disc with connective tissue so that the margin

is blurred, the lamina cribrosa is hidden, and the vessels are ensheathed in neuroglia and the disc appears shaggy.

(d) *Glaucomatous*.—The disc is white or pale-grey. The characteristic feature is deep cupping of the disc. The excavation extends to the very margin of the disc which is undermined so that there is an overhanging cornice or lip. The lamina cribrosa may be in evidence or may be obscured by neuroglia. The central vessels after passing through the lamina course over the floor of the cup, disappear under the overhanging cornice and reappear on the surface of the retina at the disc-margin, often apparently discontinuously with the earlier parts of the vessels which lie in the crater of the cup. The optic atrophy of glaucoma may be due to several factors: pressure on the nerve-fibres and ganglion-cells, kinking of the fibres at the lip of the cup and ischæmic degenerative changes at the nerve-head.

Circumference.—The disc-margin is usually well-defined but, where the retina is pale, the division is not sharply marked. In early papillœdema the disc-margin becomes blurred and often there is measurable swelling. In later stages, the swelling resembles a gelatinous mushroom and the margin is obliterated. In optic atrophy the disc-margin is clear-cut.

Crescent.—In myopia, the posterior pole of the eye is stretched, the retina and choroid give way at the temporal margin exposing a crescent of bare sclera the margin of which is often outlined by pigment. In high myopia the crescent may be larger than the disc and the sclera itself may be stretched and thinned to form a posterior staphyloma.

Contour.—In examining the disc in this connexion it is important that both of the examiner's eyes should be kept open and unaccommodated as if looking at a far distance and not at an object two inches away. The gallery of lenses is then rotated until a vessel near the centre of the disc is brought into focus with the highest possible plus-lens. The same vessel is then followed until it leaves the disc and is focused again. The difference, if any, in diopters gives a measure of the swelling of the disc. This should be carried out in vessels in different diameters, particularly where astigmatism is present. Three diopters are equivalent to 1 millimetre of swelling. Similarly, in *cupping* of the disc the base of the pit should be brought into focus, and then the retina adjacent to the disc.

Circulation.—The branches into which the central artery and veins divide lie in the nasal half of the disc. The arteries are bright red and the veins bluish-red. Pulsation of the veins at the disc is normal: but pulsation of the arteries is only seen in increased intra-ocular pressure, as in glaucoma. The arteries may be made to pulsate by finger-pressure on the globe during examination. Pulsation of the veins is a regular, gradual surging; but pulsation of the arteries, when the intra-ocular tension is increased beyond the systolic pressure, is seen as a jerky, flick-like emptying and filling of the arteries on the disc.

Lamina cribrosa.—The perforations of the sclera can be seen in many normal discs, particularly in the temporal segment, as small greyish oval markings in the pit or excavation of the disc. In glaucoma the perforations become very distinct.

Curiosities.—The disc may show unusual departures from the normal such as congenital holes; coloboma of the disc; hyaline bodies; foreign bodies such as a fragment of metal; as well as hæmorrhages, aneurysms and neuroglial proliferation.

THE BLOOD VESSELS

The retina is the only place in the living body in which blood vessels can be seen in the raw. The media of the eye and the tissues of the retina which support the retinal veins and arteries are transparent, and pathological changes in vessels, which elsewhere can only be inferred, are seen in the fundus as they take place.

Veins show many pathological variations such as general expansion or enlargement in polycythæmia; localized variations in calibre where they are crossed by a sclerotic artery; sheathing in periphlebitis and leukæmia; micro-aneurysms in diabetic retinopathy; new-formed vessels in the retina or on the disc; occlusion of the central vein as a terminal phase in phlebo-sclerosis and this is associated with hæmorrhages scattered to the extreme periphery of the fundus; and many rarer conditions such as angiomatosis (von Hippel-Lindau disease, a phakomatosis) in which the veins are grossly dilated, tortuous and aneurysmal.

Arteries.—An early sign of arterial disease is a loss of translucency of the vessel wall so that at a crossing an underlying vein does not show darkly through the artery. Then the reflex from the surface of an artery which is relatively taut and rigid is brighter than the surface-reflex from a normal vessel. Later, the artery may be accompanied by fibrous-looking white lines alongside its walls, a fibrotic perivasculitis strengthening the vessel against internal strain. Arteries and veins at their crossing are held in a common adventitial sheath and when an artery becomes thickened it takes up space at the expense of the vein which is narrowed and depressed. In long-standing hypertension the arteries become tortuous and appear to be narrowed in calibre. The central artery may become occluded with sudden loss of sight. The main trunk and its branches then appear as empty white cords and the retina surrounding the disc becomes pale and œdematous. In contrast to this pale retina, the macula, for a few hours or days, may appear as a cherry-red spot.

In general, changes in the retinal arteries indicate pathological changes in the walls of the systemic arteries, but high blood pressure is not always manifest in the retinal arteries and, on the other hand, profound changes in the retinal arteries may be found where the brachial blood pressure is

within normal limits. The appearance of the retinal blood vessels is a valuable sign but only one of many data to be considered in the clinical picture.

THE MACULA

The macula lutea is physiologically the most important part of the fundus as it subserves central detailed vision. Examination of the macula, particularly in aged persons in whom the pupil is contracted, often requires the pupil to be dilated with a mydriatic such as homatropine or 'paredrine' in a one per cent. solution. It is essential that a drop of eserine in 0.5 per cent. solution should be instilled after examination. Atropine should not be used as a mydriatic for purposes of fundus examination as its action cannot be countered by eserine.

The macula is less than two disc-diameters from the temporal margin of the disc. It is devoid of vessels and is often somewhat dusky in colour. There may be a bright spot at its centre.

Senile macular degeneration is responsible for 23 per cent. of cases of blindness over the age of 70. Loss of visual acuity or complete loss of vision may occur. The ophthalmoscopic appearances are fine stippling with pigment, small hæmorrhages and dot-like exudates. Gross exudation may be found over, or in a ring around, the macula and are described respectively as disciform and circinate retinitis. The remainder of the retina is often undisturbed so that the patient retains peripheral vision and is able to get about unassisted. The macula may also be damaged by direct sunlight as in looking at an eclipse, or by an electric-arc flash. In the latter case there may be a bright red hæmorrhage at the macula turning, months later, into an area of pigmentation. Some hereditary eye diseases are associated with macular changes and dysfunction. The ophthalmoscopic appearance of the macula does not always give an accurate indication of the visual acuity. Fine changes scarcely visible may produce central blindness whereas in changes much more evident useful vision may be retained.

THE EYE-GROUND

The colour of the fundus shows great variety. As the retina itself is transparent the colour depends upon the colour of the choroid and the retinal and choroidal pigment. The colour varies from bright orange-yellow to dusky red. In albinos, in whom retinal pigment is sparse, a tangled skein of choroidal vessels can be seen deep to the more orderly pattern of the retinal vessels and every variation is seen until we come to the dark races in which the retinal vessels scarcely stand out against the dark background.

Ophthalmoscopic examination of the retina shows an amazing variety of pictures of which in the space at disposal only a few can be indicated. First it should be stated that, as the retina is essentially neural, the condition of retinitis or inflammation of the retina is usually a misnomer. Retinitis, so-called, may be an inflammation of the underlying choroid which

involves the retina in secondary changes or it may be a degeneration of the retina to which the term *retinopathy* is more appropriate than the word *retinitis*.

Of the retinopathies, three are of prime importance: hyperpietic, renal and diabetic. In *hyperpietic retinopathy* changes in the vessels as already described are seen in the earlier stages; then small scattered hæmorrhages and small circular white exudates occur. In the final stages profuse hæmorrhages, large exudates and papillœdema (in malignant hypertension) are seen; to be followed in some cases by hæmorrhages into the vitreous and secondary glaucoma.

Renal retinopathy shows narrowing of the arteries, œdema of the retina and blurring of the margins of the disc. Flame-shaped hæmorrhages and soft masses of exudate—the 'cotton-wool patches'—are then added to the picture.

Diabetic retinopathy, which occurs particularly in long-standing cases of diabetes, is characterized by vascular changes, solid waxy-looking exudates and small punctate micro-aneurysms, which were formerly thought to be punctate hæmorrhages. There is often no clear-cut division between the various types of retinopathy; for hypertension, renal changes and diabetes may coexist.

Neoplasms.—The two commonest forms of malignant disease seen in the fundus are the retinoblastoma, formerly called glioma of the retina, and malignant melanoma of the choroid.

Finally, *retinal detachment*. This should first be examined by the indirect method to define its limits. It is typically seen as a greyish diaphanous wavy swelling upon which the retinal vessels appear as dark threads. Where there is a hole or tear the red choroid can be seen through the gap.

CONCLUSION

It may fairly be said that the clinical examination of a patient suffering from any disease, apart from a local lesion, cannot be considered to be complete without an ophthalmoscopic examination; and there is moreover the interest and fascination of 'seeing the works'.

My thanks are due to Messrs. Hamblin for figures 3 and 5, and to the Photographic Department of St. Paul's Eye Hospital, Liverpool, for figures 1, 2 and 4.

REVISION CORNER

PHANTOM LIMB

WHETHER the amputation has resulted from accident or operation, it is usual for the patient, at least for a time, to experience sensations as if the limb were still present. Such sensations may be painless or painful, but are generally more or less abnormal.

PAINLESS PHANTOM LIMB

The experiences of a minister, who had a painless phantom limb after amputation, provide a suitable clinical description.

At the age of 14 he had a mid-leg amputation and at the age of 48 he sought assistance as, ever since the operation, he had always been aware of a phantom right foot, stating that the instep and big toe were most clear and resembled the real foot although the ankle was not part of the phantom. He could 'flex and extend the foot and toes' and they were correctly placed in relation to the stump. The phantom foot was never quite normal, feeling broader than the normal foot and weather conditions affected it, so that the toes might feel crushed if it was frosty or feel immersed in moving water before rain came. He did not complain of the leg stump, which appeared normal, but continued pressure on a nerve bulb in the calf produced 'sensations' in the phantom toes.

Those who are born without digits or portions of limbs (intra-uterine amputation) never have phantom limbs, but it is true that amputation of an infant's limb may be followed by a phantom. Critchley (*L'Encéphale*, 1955, 6, 501) reports one at the age of $3\frac{1}{2}$ two years after amputation.

The story of a boy is remarkable, for as an infant he lost his right little finger and when serving in the 1914-18 War was so badly wounded in the right arm, that amputation was required. During his growing years he never had a phantom of his little finger, but after the major amputation, he had a phantom limb ending in a thumb and three fingers.

The onset is usually soon after the amputation and the disappearance is variable. General illness or trauma of the stump may cause return of a phantom.

An elderly man, who had lost the phantom connected with a thigh amputation, fractured the neck of the femur of the stump. Surgical treatment of the fracture produced a satisfactory functional result but return of the phantom.

Patients may say that the painless phantom limb feels more or less normal and gross movements may be preserved. There may even be an illusion that the hand can pass through the trunk without obstruction.

PAINFUL PHANTOM LIMB

It is noteworthy in these cases that, more often than not, the whole of the amputated portion of the limb is the phantom. The onset of pain is at the time of the appearance of the phantom and the pain is often continuous. It may be no more than an abnormal sensation—such as discomfort, an ache or cramp—or severe, being described as burning or due to great

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swelling. Fatigue and sleeplessness and a tender amputation stump may exacerbate symptoms until the pain in the phantom is comparable to that of causalgia. The pain of a cardiac affection such as angina pectoris may cause symptoms in a left phantom arm. Nerve-root irritation of the cervical or lumbar plexus may produce symptoms in a phantom corresponding to those recorded in normal limbs. It is also remarkable that the victim of paralysis agitans (Parkinson's disease) may say he has a trembling in a phantom.

THE AMPUTATION STUMP

It used to be thought that the condition of the stump had an important bearing on the existence of, and symptoms arising in, a phantom limb. It is doubtful if this is really so and it is not possible to find out if there is a smaller number of phantoms arising now in amputees, who probably have better stumps than forty years ago. Sepsis in the stump was considered to be a factor of some importance in the onset and continuance of the phantom, possibly owing to inflammation of nerves in the stump. Antibiotics have practically abolished this possible cause and dispelled the idea that it was chronic sepsis which made any phantom painful. In France, however, it is considered that if the fibro-neuromas are exceptionally tender, owing to inflammation of nerve tissue in the bulb, they do play a part in the production of pain in a phantom.

It is usual to find the stump of normal appearance, free of cyanosis, oedema and trophic ulceration, but not infrequently touching the stump or placing it in some positions may increase the pain in the phantom. When pain is severe it is usual to find the stump useless, pain being dominant over adaptive functions.

THE PATHOLOGICAL PHYSIOLOGY OF PHANTOM LIMBS

Study of this condition leads to certain realizations; that:—

- (a) in a painless phantom, the peripheral parts are represented, these having well-developed sensory end-organs capable of recording the body shape;
- (b) phantom pain results from excessive stimulation of nerve tissue;
- (c) phantom posture corresponds to that at the time of amputation, and
- (d) voluntary movement in phantom fingers and toes (and less often in larger segments) is possible.

The destruction of the cortical sensory receptive mechanism in the parietal lobe causes immediate abolition of the phantom limb. It is interesting to note that recent work reveals that phantom sensation in organs other than limbs occurs after surgical removal. Although it may be tempting to think that Nelson was right in believing that the phantom fingers of his amputated arm provided a 'direct proof of the existence of the soul', the phantom is regarded today as the expression of intactness of corporeal awareness or body image.

TREATMENT

It is more likely that a painless phantom will disappear than one that is painful.

Preventive.—Phantom limbs are experienced less when the amputation is undertaken at a hospital equipped for the postoperative treatment. Unfortunately in all countries emergency operations have to be performed at the 'nearest hospital'. Ideal conditions exist when there is a staff accustomed to postoperative treatment of the amputee, both psychological and surgical. The expert bandaging, stump exercises and functional re-education, including the provision of temporary and permanent prosthesis and walking instruction, all limit complications of an amputation.

For the painless phantom limb.—Provided there is a normal stump, it is unwise to advise any form of surgery, and psychological treatment often tends to fix or increase symptoms.

For the painful phantom limb.—So large a variety of treatments to the stump, to nerves and to portions of the central nervous system has attracted attention that a decision to operate on the brain (leucotomy or on sensory cortex), on the spinal cord or nerve roots should be undertaken only after very serious consideration.

Obviously, a stump with tender bone or nerve bulbs and periodic infection should be reconstructed, but reconstruction has no place in dealing with the pain of a phantom limb. Local injections, repeated percussion, electrical treatment or shortening of nerves with removal of bulbs sometimes relieves pain. It is difficult to understand the mode of action of sympathectomy in these cases; although results must be considered variable, some patients have been relieved of pain.

A patient having a painless or painful phantom limb should not be abandoned by his doctor, but should be provided with all the mental and physical help available, difficult though this may often be.

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THE PLASMA PROTEINS

THE plasma proteins comprise albumin, globulin and fibrinogen and amount in total to some 6 to 8 g. per 100 ml. of plasma. With the exception of fibrinogen, which must be estimated in plasma, determinations are usually carried out on serum, as the use of anticoagulants tends to draw water from the cells, to dilute the plasma, and consequently to give results lower than the true value in circulating plasma.

FRACTIONS AND ORIGIN

By 'salting-out' techniques the total protein content can be broken down into various fractions: 3.5 to 5 g. per 100 ml. albumin, 1.5 to 3 g. per 100 ml.

globulin, and from 0.2 to 0.4 g. per ml. fibrinogen. The ratio of albumin to globulin is often quoted, but in my opinion it is of little value. The absolute values of albumin and globulin are much more helpful and the important figures are the *minimum* value for albumin and the *maximum* value for globulin: any value of albumin above 3.5 g. per 100 ml. is probably normal and similarly any value of globulin below about 3 g. per 100 ml. is within the normal range.

In understanding the significance of changes in protein values in disease, the source from which the proteins are produced should be considered. The albumin and fibrinogen are entirely produced in the liver, and therefore parenchymal damage to the liver is liable to produce low values for these constituents. Globulin has a much broader source, being produced chiefly in the reticulo-endothelial system and the lymphatic tissues: hence a raised value for globulin is often met with in infections and in various forms of enlargement of the lymph glands, including lymphatic leukæmia, but this rise is not diagnostic of any specific condition.

The proteins of the plasma are not inert substances; they undergo rapid metabolic changes and are renewed and replaced very frequently under normal conditions.

So far globulin has been referred to as though it were one substance, but more recent techniques and comparatively simple applications such as paper electrophoresis have shown that 'globulin' is a very complex mixture of proteins: the globulin fractions thus isolated are described as α_1 and α_2 , β and γ globulins. For ordinary clinical purposes a simple ~~naked-eye~~ inspection of the electrophoretic paper strip and description of any increase or decrease of one of the fractions, plus an indication of any abnormal protein present, are more helpful than any attempt to elaborate values for all the globulin fractions.

THE PLASMA PROTEINS IN DISEASE

In *parenchymatous liver disease* there is often a fall in the albumin with a rise in globulin, usually shown on the paper strip as a diffuse increase in the γ -globulin region. Fibrinogen may also be diminished in liver disease.

Afibrinogenæmia or *hypofibrinogenæmia* is sometimes met with as an acute post-partum condition, and its recognition is necessary for appropriate therapy. Rapid chemical methods are available for fibrinogen estimation. Congenital afibrinogenæmia causing a form of hæmorrhagic disorder also occurs, but is an exceedingly rare condition.

In *chronic nephritis*, particularly in the nephrotic stage, the gross loss of albumin in the urine often produces a low serum-albumin figure: this is usually associated with an absolute increase in globulin, particularly of the α_2 and γ fractions.

Multiple myelomatosis is characteristically associated with a very high globulin content of the serum, and excretion of Bence-Jones protein in the urine, but either of these findings may be absent. The presence of an abnor-

malinity of serum protein is common, and shows on electrophoresis as a sharp band, unlike the diffuse increase in γ -globulin found in liver disease: this band usually occurs in the γ -globulin region, although it may sometimes occur elsewhere, or be absent.

Occasionally an abnormal protein is found which is called '*cryoglobulin*' on account of its separating from serum when this is cooled, and recently attention has been drawn to other abnormal globulins of very large molecular weight—the so-called '*macroglobulins*'. Both these appear on electrophoresis as fairly sharp bands similar to the myeloma protein. They cannot be identified with certainty except by the use of an ultra-centrifuge but, as their specific identification does not lead to any more definite therapy, this does not matter seriously.

A high serum globulin content is also often met with in *sarcoidosis*, and in some of the collagen diseases, especially systemic lupus erythematosus.

The rare condition of *congenital agammaglobulinæmia*, in which a baby may have had a series of repeated infections is recognized by the continuing complete absence of γ -globulin from an electrophoretic strip: a low content of γ -globulin, however, may occasionally occur temporarily as an unusual response to infection.

SUMMARY

It cannot be said that estimation of the serum proteins often gives a definite diagnosis of the cause of a patient's illness, but their investigation not infrequently gives a pointer to the condition to be specifically looked for, and is often of confirmatory diagnostic value.

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Director, Lewisham Group Laboratory.

NOTES AND QUERIES

Transport of Spinal Injuries

QUERY.—What is the correct first-aid treatment for suspected fracture of the spine? Originally I was taught that such a case should be carried face down in the prone position. I note, however, that the Civil Defence First-Aid Manual states categorically that the patient must be transported on his back.

REPLY.—Like most surgeons my experience of first-aid treatment of serious injuries at the accident site is limited. The first problem is the safe extraction of such injured from the debris of their accident: for example, from the smashed and badly crushed interior of a car or from the cab of a lorry—before any sort of examination is possible to ascertain the nature of their injuries. Fortunately such injured people are often unconscious during what is a major operation. At this stage care should be exercised in

preventing hyperextension or acute flexion of the spine. Ambulance crews have told me that they generally get over this difficulty by pulling the victims out either by their feet or by their shoulders. I have no personal experience of this problem.

On several occasions I have given roadside first-aid to very seriously injured people who have been thrown clear of the accident debris. It is remarkable how quietly they lie in the position in which they have fallen, with their muscles in spasm protecting the underlying bone and joint injuries. Since any added movement immediately causes a fresh spasm of pain, I have carried out my examination in such conditions leaving the victims in the original position in which they had fallen and restricted my activities to wound cover alone until the arrival of the ambulance.

The arrival of the ambulance with its stretchers

presents the next problem. How to lift patients with suspected spinal injuries on to the stretcher? This is the move that has caused considerable confusion in the instructions contained in first-aid manuals. If this *lift* is carried out by two attendants—one at the victim's knees and the other at the shoulders—hyperextension of the spine can occur with obvious danger to the cord. The old manuals therefore advocated turning the patient on his face before lifting him on to the stretcher. It is now recognized that the same type of two-attendant lift perextends the spine, itself a recognized danger to the cord in certain types of fracture—dislocation with locked articular facets. The best method is to lift the patient in the position in which he is found without preliminary moves, and on to the stretcher brought as closely to his side as possible.

As to the position of the patient on the stretcher during transport, *this should be on the back with face up*. This position allows adequate splinting of associated limb injuries, easy breathing and clear observation of the injured patient by the ambulance crew during transport. I once observed the condition of a patient immediately on his arrival at hospital after he had been transported face down on the stretcher (because it was thought that he had a spinal fracture). The lesions were subsequently shown to be a compound fracture of the femur and multiple fractures, with facial injuries. On his arrival at the hospital his respiratory difficulties were extreme and he was in a serious general shocked condition.

As a method for first-aiders the 'face down' position both for lifting on to the stretcher and subsequent transport on the stretcher in the ambulance is to be condemned.

W. GISSANE, CH.M., F.R.C.S.

Repeated Foetal Abnormalities

QUERY.—A married woman, aged 22, has consulted me on the advisability of starting a fourth pregnancy. She has had no past illnesses and her husband is also well. Their Wassermann reactions are negative and the wife is Rhesus-negative. Their first baby had a congenital heart, with malrotation of the gut, and died a few months after birth. The second baby had a normal delivery and is healthy with no known abnormality. The third baby died three days after birth—meningocele with paraplegia, and hydrocephalus.

They would like to have another child but are scared that they will have another abnormality. What are the chances of this?

REPLY.—The question as to the recurrence of foetal abnormality in a family is still a difficult

one to answer. The history given here is not complete; for example, if the mother had rubella in the first pregnancy an immediate explanation for one of the unfortunate events would be given. Similarly, it would be valuable to know if the question of consanguinity in the marriage arises.

In general, it seems to be quite definite that the chance of recurrence of some type of foetal abnormality is more likely in a family where it has previously occurred. Murphy estimated the chances as being twenty-four times greater than in the general population. Penrose found sixteen cases of deformity in 207 families where one baby had previously been born abnormal. The types of deformity stated in the case in question being dissimilar and of a recessive type would not make one advise against further children, especially as the mother is young, but it is difficult to give statistical odds on the chances.

KENNETH BOWES, M.D., M.S., F.R.C.S., F.R.C.O.G.

Dupuytren's Contracture

QUERY (from a reader in South Africa).—My wife, aged 34 years, has suffered from Dupuytren's contracture for about four years. There are marked contractions of both thenar and hypothenar eminences resulting in pain and weakness on grasping objects. She had one course of x-ray therapy in 1954, consisting of six weekly treatments of 100r each. There was marked improvement symptomatically. In March 1956, she had four treatments of 100r each, without any improvement. Her mother and paternal grandfather had marked Dupuytren's contracture. Is there any further treatment available?

REPLY.—This query presents certain unusual features. First, Dupuytren's contracture is unusual in a woman. Secondly, it is unusual to start at the age of thirty, and thirdly, involvement of the thenar eminence is extremely rare. Pain is an unusual feature in Dupuytren's contracture, and weakness in gripping is rarely complained of.

It is not possible to give any useful advice in a case such as this because of the obvious anomalous features. Ordinarily the treatment is surgical. X-rays are considered by some to be of transitory benefit but in the presence of deformity the only treatment seriously to be considered is either fasciotomy, that is to say division of the thickened bands causing the contracture, or excision of these bands together with the surrounding palmar fascia.

RONALD FURLONG, M.B., F.R.C.S.

Coloptosis

QUERY.—What does one do for a woman patient of 32 who has suffered mediocre health for the

past five years, and in whom cholecystography follow-up shows a U-shaped transverse colon sinking deeply into the pelvis with evidence of spasticity? She is asthenic, slightly constipated, and mildly neurotic.

REPLY.—It is not quite evident how cholecystography has demonstrated the transverse colon, and before advising treatment it would be wise to have a barium enema carried out to outline fully its position and to exclude any organic abnormalities. A low U-shaped transverse colon is unlikely itself to be causing any symptoms by virtue of its position, but if there is associated diverticulitis or colitis this might cause abdominal discomfort and perhaps some general ill health. It is generally agreed that any benefits which follow abdominal exercises, massage or the wearing of special belts for a dropped or low colon are due to suggestion and not to any direct effect upon the position of the bowel. Asthenia and constipation are rarely, if ever, directly due to coloptosis and it is usually wise in treatment to direct the patient's attention away from her bowel and to more general causes of her symptoms.

One of the most usual causes of long-continued mediocre health is anxiety, and if the patient is mildly neurotic it would seem best to treat this condition and ignore the position of the colon and the slight constipation. Such treatment would, of course, involve discussion and explanation of psychological causes of exhaustion, and an attempt to help the patient to adapt herself to her life and to her symptoms. Sedatives and help with sleep would in this case be more likely to help than any laxatives, 'tonics' or special diets.

THOMAS HUNT, D.M., F.R.C.P.

Morphine and Urinary Secretion

QUERY.—Is there any substantial evidence that morphine decreases urinary output by the kidneys, as opposed to causing retention of urine within the bladder? I have been advised against the use of morphine in eclampsia and pre-eclampsia on these grounds.

REPLY.—De Bodo (*J. Pharmacol.*, 1944, 82, 74) has shown that morphine decreases urinary secretion by causing release of antidiuretic hormone. It also increases excretion of oxytocin, and for these two reasons its use is contraindicated in pre-eclampsia.

PROFESSOR G. M. BULL, M.D., F.R.C.P.

Thrombophlebitis and Phlebothrombosis

QUERY.—My impression is that there is no consistent policy in the management of venous

thrombosis. The distinction between thrombophlebitis and phlebothrombosis is too hard and fast. This is recalled by some recent cases:—

A patient with a superficial thrombophlebitis in a varicose vein was treated with rest and penicillin. The thrombosis continued to extend and I asked for admission to hospital. This was refused and the patient developed a pulmonary embolus. An exactly similar case was admitted to hospital but was not put on anticoagulants until, while in hospital, she developed multiple pulmonary emboli. A third case had superficial venous thrombosis of the left leg near the ankle. She was put on partial bed rest for ten days, after which she was allowed to be ambulant. After five days on her feet she developed a fatal pulmonary embolus, apparently from deep veins in the right calf. At the time of allowing her up, there was no clinical evidence of any lesion in this area.

A final case, which I saw recently, presented a few days after childbirth with superficial venous thromboses affecting the left calf and in both thighs. She was admitted to hospital but no anticoagulant treatment was given. The patient did well. The obstetrician concerned stated that he never treated such cases with anticoagulants.

The problem of venous thrombosis is a common one in general practice. I have decided on the following policy and would appreciate your comments:—(1) If a limited area is involved, I keep the patient ambulant, and provide support and give penicillin. (2) If the lesion extends, or is at all extensive, I refer the patient to hospital for anticoagulant therapy. (3) If this is refused, and hospitals do not willingly accept this type of case, then one has no alternative but to keep the patient under constant review for possible extension of the superficial lesion or the concurrent development of deep thrombosis.

From my experience it is apparent that this policy will not always prevent the development of pulmonary emboli, and I consider that, ideally, anticoagulant therapy should be given in all cases. I would, however, appreciate the comments of an experienced physician.

REPLY.—The points raised in this query are indeed cogent. The distinction between thrombophlebitis and phlebothrombosis is not hard and fast, and often, as the reader intimates, the two conditions merge. In clinical practice most cases fall midway between the two ends of the spectrum. In many instances, venous thromboses clear up spontaneously without further extension and without causing pulmonary emboli; an example is the patient mentioned above who developed superficial thrombophlebitis.

after childbirth. In other instances, where the inflammatory component is not great, the thrombosis may extend and pulmonary emboli occur as exemplified in the first three cases cited above.

The policy suggested is sound and in keeping with modern practice. Lack of marked inflammation, extension of the disease, and involvement of more than one vein all call for anticoagulant therapy. Until this is more widely appreciated there will continue to be cases of pulmonary emboli, some of which will be fatal.

RICHARD BAYLISS, M.D., F.R.C.P.

Treatment of Lambliasis

QUERY.—What is the currently recommended treatment for lambliasis in a small child (aged three)? There is a history of recurrent diarrhoea, and cysts found in the faeces.

REPLY.—Mepacrine, 0.05 g. twice daily after meals for five days, is the recommended dosage

for a child of three. The bitter taste of the tablets can be minimized by giving them crushed and mixed with honey.

D. R. SEATON, M.B., M.R.C.P.

Non-spermicidal Lubricant

QUERY.—I have been asked by a young couple to recommend a non-spermicidal lubricant to use in order to facilitate intercourse. Is 'KY' jelly suitable or, if not, could you tell me what to suggest?

REPLY.—There are various non-spermicidal lubricants on the market. 'KY' jelly is entirely suitable although some object to its rather penetrating odour. Alternative preparations which can be recommended are 'lubafax' and 'prentif lubricant jelly'. These preparations are all water-soluble, which is a great advantage over a greasy preparation, and all would appear to be entirely non-toxic.

JOSEPHINE BARNES, D.M., F.R.C.S., F.R.C.O.G.

PRACTICAL NOTES

Nystatin in Moniliasis

The results of the use of nystatin in 122 cases of moniliasis are reported by E. T. Wright *et al.* *Journal of the American Medical Association*, January 12, 1957, 163, 92). Nystatin was used in the form of ointments, solutions, powder, troches, capsules, suppositories and jelly. The ointment and gel consisted of a plasticized petrolatum base containing 5000 to 200,000 units of nystatin per gramme of ointment base. Two types of solution, containing 5000 to 100,000 units per ml., were used. One was propylene glycol solution, and the other contained 2% procaine hydrochloride and 0.25% polysorbate 80. The latter solution was prepared both with and without 2.5 mg. of hydrocortisone per ml. The powder contained 175,000 units per teaspoon. Each troche contained 2000 units; in addition, some of them contained 2.5 mg. of neomycin sulphate and 0.25 mg. of gramicidin. The capsules and tablets that were used as troches and suppositories contained 125,000 to 500,000 units. The suppositories for vaginal use contained 10,000 to 100,000 units, and some contained the same amount of neomycin and gramicidin as the troches.

Of the 42 patients with oral moniliasis, 19 showed an excellent response and 22 a good response. Of the 17 cases of vaginal moniliasis, nine showed an excellent response and eight a good response. Of the 63 patients with cutaneous moniliasis, the results were excellent in 25 and

good in 34. In the 16 patients with cutaneous moniliasis who were treated with the solution containing hydrocortisone, the treatment period was almost 50% shorter than those treated with the solution containing hydrocortisone. In the treatment of intertriginous infections the solution was found more satisfactory than the ointment. No side-effects were observed. The period of treatment ranged from three days to one month.

Benzathine Penicillin in Syphilis

A SINGLE injection of 2.5 million units of benzathine penicillin G, in early infectious syphilis, produces results equal, if not superior, to those obtained with schedules employing 4.8 million units of procaine penicillin and aluminium monostearate, according to C. A. Smith and his colleagues (*Bulletin of World Health Organization*, 1956, 15, 1087). In the series of cases upon which their report is based they have had no failures among 52 patients treated for sero-negative primary syphilis, 27 of whom have been followed for more than a year, and 11 for more than two years. Among 67 patients with sero-positive primary syphilis, two (4%) have required further treatment: one for serological relapse and one for reinfection. Of 155 patients treated for secondary syphilis, 90 of whom have been observed for more than a year, and 47 for more than two years, the cumulative re-treatment rate was 5.5% (0.9% serological or clinical

failure, and 4.6% reinfection). The sero-negativity rates for the three stages two years after treatment are: 100% for sero-negative primary, 96% for sero-positive primary, and 94.5% for secondary syphilis. On the other hand, preliminary data suggest that a single injection of 2.4 or 2.5 mega units of benzathine penicillin may be inadequate for the treatment of asymptomatic neurosyphilis. Thus, by the eighteenth month following treatment, 21% of the patients with asymptomatic neurosyphilis treated with benzathine penicillin G had relapsed, compared with 10.5% of those treated with other penicillin G preparations.

Acetazolamide in Pre-Eclamptic Toxaemia

'ACETAZOLAMIDE ["diamox"] is a useful adjuvant to the treatment of pre-eclamptic toxæmia', according to Raymond Shanahan (*Journal of the Irish Medical Association*, February 1957, 40, 57). This conclusion is based upon the findings in 22 patients, including nine primiparæ. Patients were accepted for inclusion in the investigation if the blood pressure remained above 130/90 mm. Hg after two days' bed rest in hospital. All the patients had an initial period in hospital before acetazolamide was administered. If the nett daily fluid loss following acetazolamide was increased by more than 420 ml., compared with the control period preceding its use, ~~the result was~~ classified as 'good'. If the nett loss was increased by 280 to 420 ml., the result was assessed as 'fair'. The daily dose of acetazolamide was 250 mg. It is recommended that this dosage be maintained until the response ceases. After two days without treatment, administration is started again, and this cycle is continued for the duration of pregnancy. In this series, 'good' results were obtained in 11 patients, including five primiparæ, and 'fair' results in two (one primipara). There was no significant alteration in blood pressure, even in those who had a satisfactory diuresis. No side-effects were observed. Two stillbirths occurred in the series, but each was in a patient with a 'very severe toxæmia'.

Chlorpromazine in Malignant Disease

THE effect of oral chlorpromazine as an adjunct in the relief of pain has been studied in 76 patients by J. W. Dundee (*British Journal of Anaesthesia*, January 1957, 29, 28). 'Very good results' were obtained in subjects with malignant disease, but 'not so good results' in other types of pains. The series included 38 patients with malignant disease, 25 with 'nerve' pains, and six with osteoarthritis. Chlorpromazine by

itself possessed little analgesic value, but in conjunction with analgesics it produced satisfactory relief of pain in 32 (89%) of the patients with malignant disease. The initial daily dose of chlorpromazine was 25 mg., which was gradually increased, if necessary, to a total of 50 mg. four-hourly during the day (250 mg. daily). This total was never exceeded. The best results were obtained with a combination of chlorpromazine and levorphan. Codeine compound tablets B.P. combined with chlorpromazine gave good results in patients with moderately severe pain, and often proved more efficacious and produced less side-effects than the more powerful analgesics. Side-effects due to chlorpromazine were encountered in about two-thirds of the patients, but in only two cases were these serious enough to require discontinuation of treatment. Attention is drawn to the fact that in 10 patients pyrexia occurred during the second week of treatment, and that one of these patients subsequently became jaundiced. It is therefore recommended that serum bilirubin and alkaline phosphatase determinations and leucocyte counts be carried out at frequent intervals in patients who are having prolonged treatment with chlorpromazine.

'Nitromin' in Malignant Disease

THE effect of a nitrogen mustard analogue—nitrogen mustard -N-oxide ('nitromin')—in 19 cases of advanced malignant disease or reticuloses has been studied by B. A. Stoll (*Medical Journal of Australia*, December 15, 1956, ii, 882). This analogue is said to have the advantage of a relatively high ratio of tumour depression to marrow depression. Further, complications of nausea and vomiting are said to be minimal. There were two cases of malignant melanoma and two cases of lymphosarcoma in the series, and all four showed temporary regression of tumour masses during treatment. There was temporary regression in three of the 10 cases of advanced carcinoma. The one case of embryoma of the kidney showed no response. There was no response in the two cases of lymphosarcoma, and only a partial response in the two cases of Hodgkin's disease. The dose, orally or intravenously, is 1 mg. per kg. body weight. The usual dose for adults was 50 mg., dissolved in 50 ml. of saline, daily, either intravenously or orally at least three hours after a meal or the last thing at night. A full course generally comprises 750 mg. over a period of fifteen to twenty days. Response is often apparent after the first week of treatment.

Hypnosis for Hyperemesis Gravidarum

TWELVE cases of hyperemesis gravidarum suc-

essfully treated with hypnosis are reported by W. Giorlando and R. F. Mascola (*American Journal of Obstetrics and Gynecology*, February 1957, 73, 444). All were severe cases and all benefited from this treatment. The only pregnancy which did not result in a normal baby was that in a woman who had a spontaneous abortion at 12 weeks. Her previous pregnancy had also terminated in a spontaneous abortion—at 8 weeks. In nine cases there was relief of vomiting after one session, two patients required two sessions, and one required three sessions. Eight patients had one or more additional monthly sessions of hypnosis. Details are given of one case in which vomiting persisted after admission to hospital in spite of intravenous fluids and barbiturates. 'Strong consideration' was being given to the possibility of therapeutic abortion when, in desperation, it was decided to try hypnosis. He was able to retain fluids on the same day as the first session of hypnosis, and intravenous fluids were stopped immediately. Further hypnosis sessions were given as a prophylactic measure, and pregnancy thereafter pursued a normal course. The view is expressed that the methods of hypnosis in such cases are 'simple and can be mastered by any physician'.

34 patients with erosive arthritis, 18 were men and 16 were women (whereas both rheumatoid arthritis and psoriasis, occurring singly, are commoner in women), and that the nails were involved in 87% of the patients with erosive arthritis, compared with only 18% of those with uncomplicated psoriasis.

Urinary Calculi

In a review of the pathogenesis of urinary calculus formation, Mary G. McGeown and G. M. Bull (*British Medical Bulletin*, January 1957, 13, 53) conclude that 'the current hypothesis that stone formation is due to a deficiency of some substance which holds calcium in solution in normal urine, or to an excess of some substance with which calcium forms an insoluble complex, cannot be regarded as proved'. They consider that there is a relationship between hypercalciuria and stone formation, and that in every case of renal calculus the possibility of hyperparathyroidism, with its accompanying hypercalciuria, should be considered. They report that of 76 patients who have been investigated from this point of view, 28 have been selected for exploration for parathyroid tumours. In the 15 cases so far operated on, six tumours and four glands with histological hypertrophy have been found. The view is expressed that there is no direct evidence that infection plays any essential part in the initiation of calculi, although it seems probable that it may encourage the growth of calculi in those already predisposed to them. The prophylaxis against recurrences of calculi after surgical removal rests upon the maintenance of a high fluid intake, and the treatment of coexisting urinary infection. A high fluid intake is particularly important in the evening—to prevent a concentrated night urine.

Clubbing of the Fingers

THREE groups of patients have been analysed by Wright (*British Journal of Dermatology*, January 1957, 69, 1): 42 with psoriasis and arthritis, 55 with rheumatoid arthritis only (all these had a positive Waaler-Rose differential agglutination test [D.A.T.]), and 310 with psoriasis only. Of the first group, eight with arthritis other than 'erosive arthritis' (the term 'erosive arthritis' is used in preference to rheumatoid arthritis so that the issue may not be prejudged) showed no feature which was not applicable on the chance coincidence of the two diseases. Of the 34 patients with erosive arthritis and psoriasis, 94% had a negative D.A.T. This was taken to suggest that the combination of psoriasis and erosive arthritis is more than the coincidence of two common diseases, since the D.A.T. was positive in over 80% of patients with rheumatoid arthritis. 'It suggests that in those with a negative D.A.T. the arthritis either modified by the psoriasis, or more probably a distinct entity'. The finding of tendon sheath effusions and subcutaneous nodules (both classical manifestations of rheumatoid arthritis) in only one patient in the series—one of the 340 with a positive D.A.T.—'lends weight to the suggestion that these two were true rheumatoid patients, while the others formed a distinct group'. Two other points of interest brought out by this investigation are that of the

ANALYSIS of the clinical findings in a series of 27 patients with drumstick clubbing of the fingers, who attended the department of thoracic medicine, St. Thomas's Hospital, for a variety of respiratory ailments, failed to yield a common clinical denominator which might illuminate this association with lung disorders, according to L. Cudkovicz and D. G. Wraith (*British Journal of Tuberculosis and Diseases of the Chest*, January 1957, 51, 14). In this series not one single factor emerged which was common to all patients. This applied to age, sex, history, physical signs in lungs or heart, pulse pressure, chest radiography, bronchography, electrocardiography, respiratory function tests, haemoglobin values, and arterial oxygen saturation. This absence of a common clinical denominator

is taken to indicate the presence of an additional anomaly, and this, it is suggested, may be the formation of pre-capillary broncho-pulmonary anastomoses in abnormal lobes. Such anastomoses have been noted near lung cancers associated with painful clubbing, and it is known that clubbing disappears after excision of small lung tumours and of arteriovenous aneurysms of the lung. In three patients in the present series bilateral pre-capillary broncho-pulmonary anastomoses were associated with pulmonary hypertension. The mechanism whereby such anastomoses influence the genesis of clubbing remains a matter of conjecture.

Vitamin D Anæmia

IN reporting four cases of unexplained anæmia in adults which turned out to be the result of vitamin D intoxication, W. B. Scharfman and S. Propp (*New England Journal of Medicine*, December 27, 1956, 255, 1207) express the opinion that 'at present there seems little justification for the therapeutic use of vitamin D in a wide variety of conditions such as arthritis, allergic diseases such as asthma and pollinosis, psoriasis, acne, sarcoid and trichinosis'. In all four cases recorded the intake of vitamin D had been between 50,000 and 150,000 units daily for several years. The anæmia was uniformly normochromic and normocytic, and the hæmoglobin level varied from 8.3 to 10.75 g. per 100 ml. All four patients had varying degrees of renal failure attributed to vitamin D intoxication. The anæmia was considered to be due to the azotæmia resulting from the renal failure, but 'a direct toxic effect on the bone marrow cannot be excluded'. Treatment consists of immediate stoppage of vitamin D administration, and the administration of a low-calcium diet and a high-fluid intake. Transfusion was not required in any of the cases recorded here.

Cortisone Eye-drops

'A SIMPLE suspension of cortisone acetate powder as received from the manufacturers is not suitable for use as eye-drops', according to J. Fliteroft and M. E. Birchall (*Pharmaceutical Journal*, February 2, 1957, 178, 79). An 'elegant dispersion', however, can be obtained by the use of 'unemul', which is described as a 'smooth gelatinous form of hydrated aluminium oxide with emulsifying, wetting and suspending properties'. Finely ground cortisone acetate is triturated thoroughly with an equal proportion of 'unemul' until a smooth paste is produced. Benzalkonium chloride (0.02%), prepared by diluting a 1% aqueous solution kept for ophthalmic use, is used as the bactericide, and methylethylcellulose (0.5%), prepared from a

20% stock paste, is included as an auxiliary suspending agent. Sodium chloride, dissolved in a suitable quantity of distilled water, is then added, and, finally, the whole is made up to volume. The formula is therefore as follows:—

Cortisone acetate	1
'Unemul'	1
Benzalkonium chloride	0.02
Methylethylcellulose	0.05
Sodium chloride	0.75
Distilled water	to 100

The product is described as 'a very fine suspension, the consistency of a thin milk, which is non-irritating to the eye and is not liable to crystal growth'. Cortisone acetate, finely powdered and triturated with its own weight of 'unemul', may be stored in a tightly closed container for up to about forty-eight hours before use, when it will be readily 'wetted' by water. If this stock dispersion is stored for any longer period, the eye-drops in which it is used tend to show crystal growth after a few days.

Silver Nitrate Stains

THE following solution is said by D. J. Steward (*British Dental Journal*, February 19, 1957, 102, 143) to be 'very effective' in the removal of silver nitrate stains:—

Bichloride of mercury	10 parts
Ammonium chloride	10 parts
Distilled water	80 parts

The solution is 'equally effective either on the skin or on fabric'. The stain is rubbed briskly with gauze soaked in the solution, and the area is then rinsed in cold water.

Spasmodic Cough and Hiatus Hernia

A VIOLENT fit of coughing on lying down is described by Ch. Debray and J. P. Hardouin (*Presse Médicale*, February 2, 1957, 65, 207) as an important diagnostic symptom of hiatus hernia. The usual story is that the patient gets off to sleep quite easily, but is awakened up, usually in the small hours of the morning, by a violent spasmodic fit of coughing, which compels him to sit up in bed to obtain relief. The bout usually lasts for only a few minutes, and the patient then settles down to sleep for the rest of the night. It is not accompanied by any expectoration. Not infrequently it is accompanied by heartburn and waterbrash. Patients who are subject to this spasmodic cough often find that one particular position in bed tends to bring it on. Thus, some are only subject to it when they lie on the back, whilst others experience it when they lie on either the right or the left side. The cough is attributed to regurgitation of the gastric contents irritating the glottis.

REVIEWS OF BOOKS

Symposium of Tuberculosis. Edited by F. R. G. HEAF, M.D., F.R.C.P. London: Cassell and Co. Ltd., 1957. Pp. xvi and 755. Figures 54, plates 78. Price £5 5s.

ALTHOUGH it will be valuable to the tuberculosis worker in Britain, clearly Professor Heaf has edited this book with a much wider public in mind: in areas of the Commonwealth and the Colonies where tuberculosis control is less established. He implies this aim in his foreword and the dust cover refers to 'countries where the tuberculosis morbidity and mortality rates remain high'. This perhaps is one reason for giving detailed mention to some methods of treatment, for instance artificial pneumothorax, which have lost popularity in this country. Although the indications and techniques of active treatment are well covered on the whole (very little is said, however, about methods of assessing respiratory function, and the treatment of tuberculous meningitis is scantily dealt with; e.g. there is no mention of isoniazid), they occupy only four chapters—including those on non-respiratory and children's tuberculosis—out of the thirteen. There is no section on pathology as such. The construction is therefore different from that of most books on tuberculosis and is exceptional in its detailed attention to the over-all picture.

Naturally, such a symposium could not be compiled without including the personal views of the collaborators (possibly most obvious in the chapter on non-respiratory tuberculosis), but generally they will be found balanced and acceptable. The admirably factual chapter on tuberculosis in industry might have been improved by a discussion on methods of combating the disease in this field. The introduction, which the editor himself writes, is of great interest as a summary of the conclusions of one who must be unique in his experience of the tuberculosis problem in so many countries. The short 'plan of approach' which occupies some three pages towards the end of this introduction gives a ground plan for anyone starting to assess the problem in a community. This is a book which physicians interested in public health or tuberculosis anywhere ought to possess and study.

Modern Trends in Geriatrics. Edited by WILLIAM HOBSON, M.D., D.P.H. London: Butterworth & Co. (Publishers) Ltd., 1956. Pp. vii and 422. Figures 68. Price 72s. 6d.

THIS symposium deals with a wide variety of subjects of practical importance in the treatment

of the elderly. Some of the outstanding contributions are: 'Arteriosclerosis and Hypertension' by Dr. F. H. Smirk, 'Chronic Bronchitis' by Dr. F. J. Flint, and 'Orthopaedic Surgery' by Mr. Cecil Flemming. A summary of the therapeutic agents used in the treatment of the common conditions encountered in the elderly is given by Professor G. M. Wilson. Dr. J. H. Sheldon's account of 'Problems in the Home Care of the Elderly' is most stimulating and indicates the need for a more careful clinical investigation into the common causes of disability in old age. Those responsible for the future planning of the geriatric services will find much useful advice in Dr. W. Morton's chapter on hospital care.

Professor Hobson and the other contributors are to be congratulated on producing a book which will be of great interest to general practitioners, hospital physicians, medical officers of health and administrative medical officers.

Pulmonary Emphysema. Edited by ALVAN L. BARACH, M.D., and HYLAN A. BICKERMAN, M.D. Baltimore: Williams & Wilkins Co.; London: Baillière, Tindall & Cox, 1956. Pp. x and 545. Illustrated. Price 80s.

THIS is certainly the most comprehensive book that has been written on this subject. It falls into two halves. In the first there are eight chapters on the causes and on the management of emphysema, as carried out at the Presbyterian Hospital, New York, by the editors and Dr. Gustav Beck. The relative lack of emphasis on chronic bronchitis as the forerunner of emphysema may surprise English readers, although full emphasis is given to the importance of exacerbations of infection in causing respiratory failure. The importance of using oxygen with caution to avoid undue respiratory depression is stressed. There is naturally a good deal about the use of helium mixtures, positive-pressure breathing and the various machines for assisting both respiration and cough for which Dr. Barach is well known, and a whole chapter, perhaps rather uncritical, on breathing exercises and other methods to 'restore' diaphragmatic function. The use of bronchodilatation, postural drainage and adrenal hormones is fully discussed but again with rather more enthusiastic claims for success than can readily be accepted by those with experience of the intractable cases which are not infrequent. The second half of the book contains seven chapters on various aspects of the disturbances of pulmonary function encountered in emphysema, written by acknowledged experts, but in

a manner which is easy to follow. There are also chapters on the treatment of bronchial infection and on various surgical procedures—which are not considered to be effective except for resection of localized overdistended bullæ.

This book will be a valued addition to the shelves of the many doctors who are becoming concerned with the fascinating etiological, functional and therapeutic problems presented by emphysema. For the busy practitioner the practical chapters are too verbose and optimistic whilst much of the theory is as yet irrelevant to practice. The bibliography, although almost exclusively American and British, is extensive.

Outline of Fractures. BY JOHN CRAWFORD ADAMS, M.D., F.R.C.S. Edinburgh: E. & S. Livingstone Ltd., 1957. Pp. vii and 248. Figures 218. Price 27s. 6d.

MR. ADAMS has followed up his excellent 'Outline of Orthopædics' by a companion work on fractures. Every word is carefully selected so that with remarkable conciseness one is given a very readable compendium. It will prove a valuable guide not only to senior medical students but, equally important, to general practitioners for, as the author states, the latter 'must know upon what evidence he should suspect and recognize a fracture; he should know the general principles of treatment so that he may advise his patients intelligently in the intervals between their visits to the fracture clinic; and he should know the complications that are liable to arise'. A copy should be in every hospital casualty department: a worthy companion to more voluminous works. A feature of particular delight is the clarity, simplicity and practical value of the illustrations.

New Bases of Electrocardiography. BY DEMETRIO SODI-PALLARES, M.D., with the collaboration of ROYALL M. CALDER, M.D. London: Henry Kimpton, 1956. Pp. 727. Figures 523. Price £6 15s.

IN the opinion of the reviewer, this is the most successful attempt which has yet been made in the English language to remove clinical electrocardiography from its still mainly empiric position and set it on a scientific footing. The author is particularly well qualified to write such a treatise and has contributed much that is original to the subject. He was the first to record cavity potential from the human left ventricle and has, in fact, devoted a whole chapter to intracavity recordings.

In such a short review it is difficult to single out particular sections for special mention, but the description of cardiac infarction is certainly outstanding, and a fascinating account of the

activation process in the human heart is given. There is also a good summary of present knowledge concerning vectorcardiography. Perhaps the most valuable part of the work is the appendix, in which the author has drawn together from widely scattered sources many of the mathematical formulæ used in electrocardiography and has explained their derivation and practical application. On the debit side, although nearly one thousand references are listed all too few are British. Considering that the work is by no means a complete account of electrocardiography, for example the arrhythmias are hardly mentioned as such, the price is high even for these days.

The translation from the Spanish by Dr. Calder is brilliant, and he has succeeded in making most readable this very technical book.

Fluid Balance Handbook for Practitioners. BY WILLIAM D. SNIVELY, Jr., M.D., and MICHAEL J. SWEENEY, M.D. Oxford: Blackwell Scientific Publications, 1956. Pp. xix and 326. Figures 27. Price 51s.

THERE are many books on body fluids but few are as effectively written for the practitioner and the non-expert as this one. The authors have, to use an Americanism, fallen over backwards to present the intricacies of salt and water metabolism in a comprehensible, easily read form. They have been outstandingly successful and their desire for simplification has not led to too many errors of fact. Thus, although likely to be remembered, it is not entirely acceptable to state that a reduction in electrolyte concentration of the extracellular fluid causes the cells to be filled 'to the bursting point with water'. Some of the more turgid prose in the earlier chapters—'Human extracellular fluid, that salty liquid which bathes our body cells, is truly an ancient fluid. Its primordial ancestor was ocean water of the Paleozoic seas of a third of a billion years ago. It was during this period that the remote ancestors of the human race forsook their marine homeland and ventured ashore to populate the greening continents'—may be displeasing to English, in contradistinction to American, readers but is readily forgotten and forgiven because the book is so good.

In Their Early Twenties. BY PROF. T. FERGUSON and J. CUNNISON. London: Oxford University Press, 1956. Pp. vi and 110. Price 12s. 6d.

THIS is the continuation of the story of 1,349 Glasgow schoolboys who left school in 1947 at the earliest permitted age, who were studied between 14 and 17 in the book 'The Young

Wage Earner', who have now completed or been rejected for military service, and whose careers during the subsequent two years until 22 is known. Over 500 cases were studied. Approximately 40 per cent. were rejected for military service, and these men came from homes of unskilled manual workers. Although poor physique was such a handicap, by 22 they had settled to their jobs better than the ex-enlisted, and their small crime rate was no worse than that of the ex-soldier, and much better than it had been before 18. The R.A.F. man had had a better personality assessment, physique and background than his Army opposite; a point suggesting more satisfactory screening. And he will get a more skilled job on discharge, and will be more likely to return to his old job than the ex-soldier. He will (provided he comes from this group) escape unemployment more easily than the military man, or the reject. When he is demobilized he is almost four times as likely to join an organized group, games or club. But only 4 per cent. attend evening classes. There is a regrettable tendency for apprenticeships to be given up after return from the Services, and the years there do not encourage men to a life more full of foresight upon discharge. It seems regrettable that of the 20 per cent. who found settling down so difficult, many come from the new estates. Improvement in social conditions seems no guarantee that contentment will follow.

This small volume is to be commended for the light it sheds upon the problems of the young man and his adaptation to a society which, even with full employment elsewhere, allows 6 per cent. unemployment among these men at so impressionable a period of their lives.

Anatomical Techniques. BY D. H. TOMPKETT, B.Sc., PH.D. Edinburgh: E. & S. Livingstone Ltd., 1956. Pp. xvi and 240. Figures 83. Price 35s.

It is fitting that a book concerned with the techniques of production of anatomical specimens should be written by a member of the Royal College of Surgeons of England, which houses the 'John' half of the world's most famous anatomical museum, collected together by the two Hunter brothers. This book gives practical instruction—which can be followed by an intelligent museum technician—on the methods of preparing different types of anatomical specimens. Part I deals with the fixation and injection of dissected specimens together with instruction regarding how and where to mount them. There is a smaller section concerned with the illustration of specimens, incorporating useful advice to the medical artist. The author has made a special study of the

production of 'casts', in particular, those of the bronchial tree, heart, blood vessels and brain cavities, and naturally the largest section of the book is devoted to description and instruction in this specialized technique. There is the timely warning that there is a period of trial and error before the tyro can hope to produce the beautiful specimens illustrated in the book. A final brief section on that colourful show-piece, the stained brain slice, is followed by a useful appendix on how and where to obtain the necessary materials.

A book which is a record of personal experience and achievement and which should be read by all interested in the collection and presentation of biological material.

The History of the School of Tropical Medicine in London. BY SIR PHILIP MANSON-BAHR, C.M.G., D.S.O., M.D., F.R.C.P. London: H. K. Lewis & Co. Ltd., 1956. Pp. xiv and 329. Figures 30. Price 50s.

THIS, Memoir No. 11 of the London School of Hygiene and Tropical Medicine, is a most enjoyable history, written by a man whose personality enlivens every page. Sir Philip's intimate knowledge and obvious love of the School qualify him before anyone alive to write this book. He recounts how Sir Patrick Manson, against powerful opposition, founded the School with the support of Joseph Chamberlain. He shows how the great discoveries of the early days, which have helped to establish health in the tropics, were achieved in an institution where the biological and clinical sciences were closely linked. He regrets their present separation, and there are no examples better than his to demonstrate their potential cross-fertility. The second half of the book consists of the biographies of the workers at the School, all of whom the author has known personally. There is also an interesting appendix in which are listed the publications of the staff and the diseases encountered in London at the Hospital for Tropical Diseases.

NEW EDITIONS

The Essentials of Modern Surgery, edited by R. M. Handfield-Jones, M.C., M.S., F.R.C.S.; and Sir Arthur E. Porritt, K.C.M.G., C.B.E., M.Ch., F.R.C.S., in its fifth edition (E. S. Livingstone Ltd., 75s.).—Every medical student needs a textbook sufficiently complete to cover every aspect of surgery and the surgical specialties, sufficiently simple to be clear, yet sufficiently authoritative and up to date to deal with any questions that may arise during clinical work or that may be asked at examination. Handfield-

Jones and Porritt' has long stood high in this category. With more than 1200 pages it is the equivalent of a two-volume work, but it has the advantage of single-volume compactness. Although the book was first published nearly twenty years ago, and has gone through four editions and as many reprints, this is the first occasion on which it has undergone a major revision. The whole work has been brought up to date—indeed, largely rewritten. The illustrations are particularly well chosen. As a general textbook of surgery it can be recommended with confidence to undergraduates and postgraduates alike. But why is the Bunyan bag referred to on page 142 as the Stannard envelope? John Bunyan was the inventor, Stannard the manufacturer.

Sequeira's Diseases of The Skin, in its sixth edition (J. & A. Churchill Ltd., 105s.) has been revised by J. T. Ingram, M.D., F.R.C.P., and R. T. Brain, M.D., F.R.C.P., who collaborated with Dr. Sequeira in the preparation of the fifth edition. The chapter on leprosy has been written by Dr. R. G. Cochrane. This new edition maintains all the important attributes of earlier editions—a sound, predominantly clinical review of the subject, in which the authors are at pains to integrate the subject with general medicine. The majority of the 426 illustrations and the 63 coloured plates are admirably reproduced, although perhaps a little more radical pruning would have been helpful. This remains one of the best books on the subject for the general physician—whether in consulting or general practice.

A Companion in Surgical Studies, by Ian Aird, M.Ch., F.R.C.S., in its second edition (E. & S. Livingstone Ltd., 84s.) is the notebook of a man who has spent his life in teaching surgery to postgraduate students. He is a hard worker and has an unusual gift for clear writing. The book has earned such a reputation that the man who would contemplate working for a Fellowship in surgery without buying or borrowing a copy would be looked on by his fellows as almost certifiable. The new edition, which contains much new material, will be sure of a warm welcome.

The Diseases of Occupations, by Donald Hunter, M.D., F.R.C.P., in its second edition (English Universities Press Ltd., 105s.) appears only two years after the first edition. This in itself is striking tribute to its quality. In this edition new sections have been added on thallium poisoning, on iron and steel foundries and on the hazards of work in sewers, and the sections on poisoning by cadmium, manganese and vanadium have been brought up to date. There are many other textbooks on industrial diseases, but there is

none other which has the historic sweep, the clinical approach or the terseness of style of this one. 'Hunter on Occupational Diseases' will long remain a classic. The illustrations (there are over 400 of them) are among the outstanding features of the book. It is all the more the pity therefore that the standard of reproduction is not equal to the skill shown in their selection.

Blood Transfusion in Clinical Medicine, by P. L. Mollison, M.D., M.R.C.P., in its second edition (Blackwell Scientific Publications, 45s.) has been enlarged by 100 pages to include the principal advances in transfusion practice and technique of the past five years. Outstanding among many new sections are: methods for the determination of red cell survival and red cell mass employing radioactive chromium, the prolonged storage of red cells in the frozen state, transfusion of the injured patient, and hæmolytic disease of the newborn resulting from mother-child ABO incompatibility. Clinicians and pathologists will find that this book contains a clear, authoritative and up-to-date account of all aspects of blood transfusion, and it can be recommended as the best available on this subject.

Clinical Pathology: Applications and Interpretation, by Benjamin B. Wells, M.D., Ph.D., in its second edition (W. B. Saunders Co., 59s. 6d.) represents an extensive review of the original volume which appeared in 1950. The general arrangement of each chapter has been preserved, but in some instances sections have been enlarged and rearranged: for example, consideration of viral and rickettsial diseases now appears at great length and in a more prominent position. New material is also incorporated, as for example on hypersplenism, radioiodine, electrolytes and water balance, and the significance of 17-ketosteroids. The final chapter, which in the original volume was an appendix dealing with laboratory aids in symptom diagnosis, e.g. sputum examination, now contains a more extensive reference to such laboratory procedures as can be readily carried out in the 'ward laboratory'. Not the least valuable feature of this excellent book is what A. H. Sanford in the preface calls the 'philosophy of the author in his introductory considerations'. This is the feature which makes the book particularly suitable to the clinical unit where there is always a need for helpful guidance on the application and interpretation of laboratory methods.

The contents of the May issue, which will contain a symposium on 'Diseases of the Eye' will be found on page A108 at the end of the advertisement section.

Notes and Preparations see page 515.
Fifty Years Ago see page 519.
Motoring Notes see page A87.
Travel Notes see page A91.



'MEPAVLON', I.C.I.'s new tranquilliser, is distinguished by its ability to relieve both mental and muscular tension without dulling consciousness. It has proved to be particularly suitable for calming the nervous patient troubled with anxiety, restlessness and irritability. In such cases, 'Mepavlon' stabilises the emotions, relaxes tension and relieves nervous insomnia by inducing natural sleep. No less important: its toxicity is low, it is well tolerated, and side effects are rare.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

'DELTALGYCORTRIL' tablets each contain 0.5 mg. of 'deltacortril' brand prednisolone and 300 mg. of aspirin, and are for use in 'controlling symptoms in less severe rheumatic and arthritic conditions'. Issued in bottles of 100 tablets. (Pfizer Ltd., 137-139 Sandgate Road, Folkestone, Kent.)

'LOCAN' pessaries each contain amethocaine, 10 mg.; amylocaine, 5 mg.; solution of benzalkonium chloride B.P.C., 0.02 ml.; lactic acid, 30 mg., and lactose, 250 mg., and are intended for the treatment of trichomonal, monilial and non-specific vaginitis and cervicitis. They are said to 'provide an immediate soothing action with rapid control of infection and the restoration and maintenance of the normal vaginal physiology' and to incorporate 'a new type of base which rapidly melts and diffuses, but does not leak, stain or soil clothing'. Issued in boxes of 12 and 72 pessaries. (Allied Laboratories Ltd., 140 Park Lane, London, W.1.)

'NITENSAR' tablets each contain quinalbarbitone sodium, 12.2 mg.; pentobarbitone sodium, 12.2 mg.; butobarbitone sodium, 4 mg.; phenobarbitone, 4 mg.; and reserpine 0.1 mg., and are indicated 'whenever gentle tranquilization is considered beneficial to the patient'. They are said to act within 20 minutes, to produce 'smooth, consecutive deepening of the calming effect'. Issued in bottles of 50, 100 and 1000 tablets. (Armour Laboratories, Hampden Park, Eastbourne, Sussex.)

'PENAVLON' V tablets each contain the equivalent of 120 mg. (free acid) of penicillin V (phenoxy-methylpenicillin), equivalent to 200,000 units of penicillin G. Issued in tubes of 15 and bottles of 100 and 500 scored tablets. (Imperial Chemical Industries Ltd., Pharmaceuticals Division, Fulshaw Hall, Wilmslow, Cheshire.)

PHARMACEUTICAL NOTES

CAMDEN CHEMICAL CO. LTD. announce that they are now marketing 'cafron' brand benactyzine hydrochloride in tablets of 1 mg. (sugar-coated). Issued in bottles of 100 and 1000. (61 Gray's Inn Road, London, W.C.1.)

PFIZER LTD. announce that their nasal decongestant 'tyzanol' is now available in a paediatric concentration for use in infants and in young children under six years of age. Issued in bottles containing 15 ml. of 0.05% tetrahydrozoline hydrochloride, with calibrated droppers. (137-139 Sandgate Road, Folkestone, Kent.)

ROUSSEL LABORATORIES LTD. announce that 'hydrocortisyl' skin spray has been added to their range of hydrocortisone preparations, in the form of a 'pressurized $\frac{1}{2}$ % solution', supplied in bottles of 100 ml. (847 Harrow Road, London, N.W. 10.)

COURSES AND CONFERENCES

THE *Seventh International Cancer Congress* sponsored by the International Union Against Cancer will be held in London from July 6 to 12, 1958, under the presidency of Sir Stanford Cade. Full details and enrolment forms may be obtained from the Secretary, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W.C.2.

Chest Diseases and the Family Doctor will be the subject at a weekend intensive postgraduate course for medical practitioners, to be held in Norwich on April 13 and 14, 1957. Details may be obtained from the Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W.C.1.

The Child and His Home will be the subject for discussion at a summer school organized by the British Social Biology Council, to be held at the Cité Universitaire, Aix-en-Provence, France, from August 24 to September 8, 1957. Further information may be obtained from the British Social Biology Council, Tavistock House South, Tavistock Square, London, W.C.1.

FILM NEWS

The Diabetic Diet (16 mm., commentary; running time 15 minutes) is intended as an aid to the instruction of diabetics and those who care for them. Produced by Eothen Films in cooperation with the Medical Advisory Committee of the British Diabetic Association and written and directed by Philip Sattin. On free loan from the Paramount British Film Library, Aintree Road, Harehale, Greenford, Middlesex.

RADIOACTIVE ISOTOPES IN MEDICINE

A COURSE on *Radioactive Isotopes in Medicine* will be held in Sheffield and London from September 15 to 28, 1957, for overseas qualified medical practitioners who are proficient in English. Further details may be obtained from the local representative of the British Council or, for those resident in the United Kingdom, from the Director, Courses Department, The British Council, 65 Davies Street, London, W.1.

MEDICAL RESEARCH IN SCOTLAND

THE Scottish Hospital Endowments Research Trust, which administers a sum in excess of £2 million, formerly part of the funds of Scottish voluntary hospitals, has just published its first annual report, covering the period January 12, 1954, to July 31, 1955. Its funds give it an annual income of the order of £90,000, but experience shows already that this may be less than adequate if all promising projects are to be assisted. The trustees are empowered to hold and administer further sums and, in a letter accompanying the annual report, Sir John Maxwell Erskine, the chairman of the Trust, expresses 'the hope that this will be kept in view by Scottish people who have a long-standing tradition of making donations and bequests for scientific purposes in this field'. The address of the Trust is 12 Hope Street, Charlotte Square, Edinburgh, 2.

THE INSTITUTE OF PSYCHIATRY

THE annual report of the Institute of Psychiatry of the University of London for the year ended July 31, 1956, contains details of an examination of the records of 11,000 patients admitted during 1947-49 to the two largest observation units in London and to certain mental hospitals serving the metropolitan area. Of the 9000 patients admitted to the observation units, just over a quarter recovered quickly from a short-lived disturbance and were able to return home in two or three weeks. Seven per cent. of those admitted died in the observation units. From the first admission rates it is calculated that, out of every thousand babies born, 53 will be admitted at least once in their life to a mental hospital; 10 of these will suffer from schizophrenia, 11 from manic-depressive and involutional psychoses, and 24 from psychoses of old age.

The investigation also showed that single persons are more likely to enter mental hospitals than married persons, and once in they are less likely to reach the point at which they can be discharged. Thus, in the group of men aged between 30 and 49, the number of first admissions per million was 1,455 (± 196) for single men and 299 (± 38) for married men; the corresponding figures for women were 1,262 (± 173) and 536 (± 52). Of the schizophrenic patients admitted, 60% were discharged within a year. During the follow-up period of 3½ years, a third of the schizophrenic patients were re-admitted at least once. 'In spite of recent advances in treatment, there are still many patients who have had to spend years, and perhaps the rest of their lives, in a mental hospital'. Of the patients in such hospitals on

any given day, 85% have been there at least one year, 77% for two years, 64% for five years, and 48% for ten years.

CHIROPODY FOR OLD PEOPLE

OF the 208 applications for grants received by the National Corporation for the Care of Old People during the year ended September 30, 1956, 193 were for assistance for chiropody schemes for old people. Many more requests for help for such schemes were received, but they had to be refused because of the limitation of funds allocated for this purpose. Attention is drawn to the fact that the Ministry of Health has recognized as competent to operate in the National Health Service only chiropodists whose standard of training reaches an approved level. This excludes many who practise chiropody after receiving their training by correspondence course. A plea is made in the annual report of the Corporation for reconsideration of this question of standards. In the opinion of the Corporation, 'this question of standards—in spite of the many inherent difficulties—and of numbers is one the Governors believe is even more important than that of finance'.

NATIONAL LIFE TABLES

THE 'Life Tables' volume of the 'Registrar General's Decennial Supplement, England & Wales, 1951' (H.M. Stationery Office, price 3s.) show that the expectation of life for a boy at birth has increased by nearly 15 years in the past forty years; for a girl the increase is more than 16 years. In 1910-12, 120 of every 1000 boys born and 98 of every 1000 girls born died before reaching their first birthday; the corresponding figures for 1950-52 were 33 boys and 25 girls. In adult life, women are still faring better than men. At age 60, for instance, the expectation for men on 1950-52 mortality is about 14½ years, an increase of only ½ year on the figure twenty years earlier, whereas for women it is now 18 years, an increase of 1½ years in this period. Persons living in England have a higher expectation of life than those living in Scotland or Wales. There are considerable variations between different parts of the country. In the Merseyside conurbation, for example, the mortality for men was 21% above the national average, whilst in the Eastern region (mainly rural) the mortality for men was 14% below the national average.

MEMORIAL TO
SIR ALEXANDER FLEMING

THE townspeople of Darvel, Ayrshire, have raised £2,500 to provide a memorial to Sir Alexander Fleming, who was born there in

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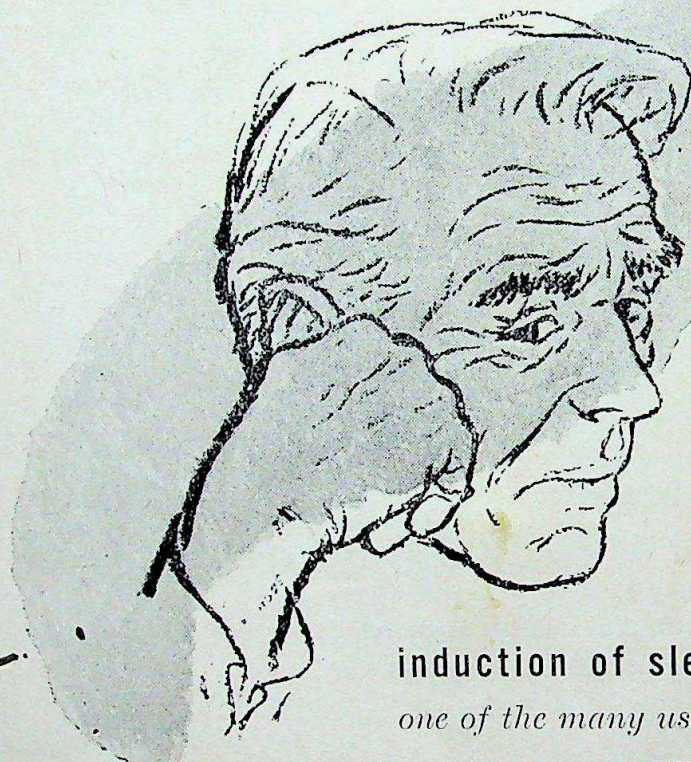
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1. *Wis. med. J.* (1954) 53:32
2. *Amer. J. Obstet. Gynec.* (1954) 58:201
3. *J. Indiana med. Ass.* (1954) 47:869
4. *J. Clin. Endocr.* (1955) 17:272

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1881. To this sum five British manufacturers of penicillin have added the sum of £2,100. Plans for the memorial include the provision of a clinic or a research scholarship, and the erection of a notice at the entrance to the town marking it as Sir Alexander Fleming's birthplace.

THE WELFARE BOOMERANG ?

THE following is an excerpt from the annual report for 1956 of Dr. John Maddison, the medical officer of health for Twickenham. 'In the infant welfare clinics we have been noticing that a number of younger mothers seem to complain more of fatigue than their mothers used to do. These younger women are those with one or two young children; they usually come from good homes where the standards are high. I wonder if the struggle for the maintenance of high standards of health and well-being; the possession of a good home and furniture, the keeping up of appearances with the neighbours; the maintenance of a high standard of infant and child welfare; the pressure on all sides from the welfare services, women's magazines, and other sources of information and teaching, whether all these tend to exhaust our mothers too much. Forty years ago, I fancy our mothers weren't so well informed; so I wonder if the fatigue is due to the pressure of modern life, or do our present-day standards demand too much? We must not let our quest for excellence be so strong and enthusiastic as to be inimical to the welfare of those for whom it is intended'.

MEAT CONSUMPTION

New Zealanders are the biggest meat eaters in the world, according to some recently published figures for world consumption of meat. In 1955, they ate an average of 216 pounds (98 kg.) per head. Australians came next, with an average consumption per head of 211 pounds (96 kg.). The comparable figure for the United Kingdom is 128 pounds (58 kg.), compared with an average of 109 pounds (46 kg.) for the five-year period before the War. The United States and Canada ranked fifth and sixth, their consumption being 101 pounds (73 kg.) and 146 pounds (66 kg.) respectively.

CLEANSING OYSTERS

Since it was established in 1934, the Brighton-Purification Station has treated 46 million oysters, valued at over £700,000 (at 1956 prices) without a single case of illness attributed to their consumption. This excellent record has been maintained in spite of topographical and bacteriological evidence that the oysters from this locality may be heavily polluted. In reporting

these figures, P. C. Wood, of the Ministry of Agriculture, Fisheries, and Food Fisheries Laboratory, Burnham-on-Crouch (*Publ. Hlth (Lond.)*, 1957, 70, 92) gives details of recent changes in the methods of treating oysters which have resulted in considerable financial saving. For long it was considered that the ability of oysters to cleanse themselves was reduced at low water temperatures, and a minimum water temperature of 54° F. (12.2° C.) was adopted at Brightonsea. Subsequent investigations have shown that a temperature of 41° F. (5° C.) is adequate. This means that the treatment water has now to be warmed for only a few weeks, instead of regularly each year from September to May.

PROFESSIONAL FOOTBALLERS' I.Q.

PROFESSIONAL footballers are more intelligent than the people who watch them play, according to French psychologists as a result of an investigation they have carried out on 108 professional footballers. The investigation was made at the request of the French Football Federation which is trying to find out how to place footballers when they become too old to play or have to retire because of injuries. The investigation showed that the average footballer's intelligence quotient was noticeably higher than that of spectators, the I.Q. of the latter being based upon figures for the 'average Frenchman'.

COMMUNICATION THROUGH ART

'Communication through Art' is an exhibition of pictures executed as occupational therapy by patients in mental hospitals. Its purpose is to provide psychiatrists who have not previously made use of painting with an opportunity of assessing its possible worth in their own relationships with patients. It is available for showing at any mental hospital. Superintendents of such hospitals, who are interested in the matter, can obtain full details from William R. Warner & Co. Ltd, Power Road, London, W.4, who will be pleased to make arrangements for the transport of pictures and setting up of the pictures.

PUBLICATIONS

The Treatment of High Blood Pressure, by F. H. Smirk, M.D., F.R.C.P., is the George Alexander Gibson Lecture delivered before the Royal College of Physicians of Edinburgh last year. Although the lecturer reaches the somewhat depressing conclusion that 'the skill and time expenditure required to dodge side-effects make it evident that the drugs we have available at present are far from ideal', his account of the

ganglion-blocking drugs will be read with profit by all clinicians. (The Royal College of Physicians of Edinburgh, price 3s. 6d.)

Looking after Old People at Home, by Doreen Norton, S.R.N., is an excellent practical guide to the subject, written for relatives and friends who have to look after old people. Practitioners are strongly advised to obtain a copy, not only for their own benefit, but also so that they can recommend it in suitable cases in their practices. (The National Council of Social Service, price 2s. 6d., or 2s. 10d. post free.)

You and Your Baby, which is described as a 'Family Doctor Special', is an admirable guide to the subject written by a host of experts, including Professor J. C. McClure Browne, Professor Dugald Baird, Professor R. S. Illingworth, Dr. A. P. Norman and Dr. Dermot MacCarthy. It is not on sale in the ordinary way and is being distributed only by doctors to their patients. Bulk prices can be quoted to doctors only, on application to *Family Doctor*, B.M.A. House, Tavistock Square, London, W.C.1.

Dental Health, edited by Professor H. H. Stones, M.D., M.D.S., F.D.S. R.C.S., is an excellent book meant primarily for teachers, parents and other 'educated laymen'. There is a full glossary, including a little Greek. More than sixty photographs and diagrams, mostly in colour, add to the clear descriptions dealing with the anatomy and development of teeth, common dental diseases and their prevention by diet and sensible rules for the nursery and schoolroom. One small criticism: a child with mouth-breathing (p. 67) should be seen first by the family doctor, not referred direct to an E.N.T. specialist. (The Dental Health Board of the United Kingdom, price 10s. 6d.)

The Christchurch Hospital Medical Manual, edited by C. T. Hand Newton, D.S.O., M.D., F.R.A.C.P., F.R.C.S.ED., in its fourth edition is essentially designed for the use of students and house officers of the Christchurch Hospital, in order to obtain a measure of uniformity in administrative clinical routine. For this purpose sections are contributed by the pathological, x-ray, dietary and other departments. Apart from its purely local features, the general principles of which might well apply in any large hospital, the information concerning pathological investigations and their interpretation, special diets and many other details is clear and accurate and would be found universally valuable. It is a good little book of its kind and has been thoughtfully and carefully prepared. (N. M. Peryer Ltd., and Lloyd Luke, price 27s.)

OFFICIAL PUBLICATIONS

Health Services in Britain is one of a series of pamphlets produced by the Central Office of Information for the Overseas Information Service. It provides a factual account of the subject which will be read with interest by many in the United Kingdom as well as abroad. Needless to say, it paints as rosy a picture as possible of the National Health Service, but there has been a laudable attempt to maintain a reasonable degree of impartiality. (H.M. Stationery Office, price 3s.)

Health Education (Ministry of Education pamphlet 31) is described as 'a handbook of suggestions for the consideration of teachers and others concerned in the health and education of children and young people'. Fortunately the contents are not in the same tradition as the photograph which 'graces' the cover, and it is a pamphlet which can be unreservedly commended to all concerned with this important subject. (H.M. Stationery Office, price 4s.)

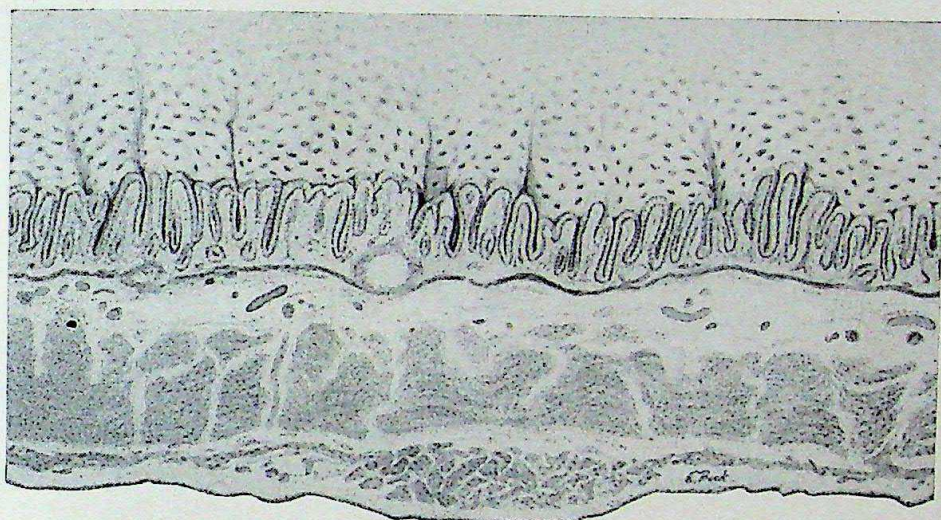
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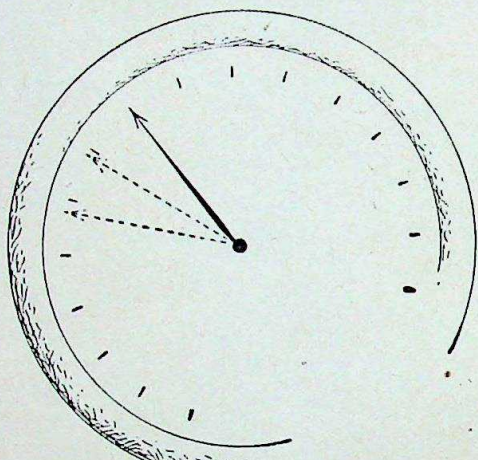
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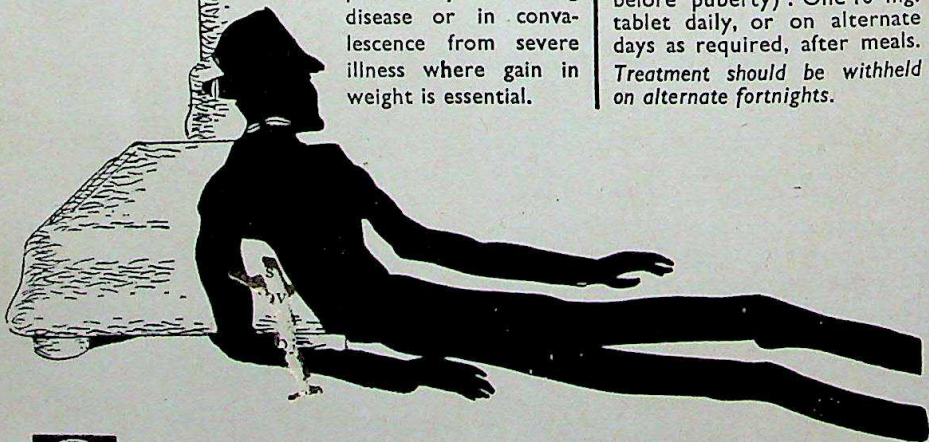
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THE PRACTITIONER

Fifty Years Ago

'Man is a machine into which are put what we call food and produce what we call thought'.—R. G. Ingersoll: *The Gods*.

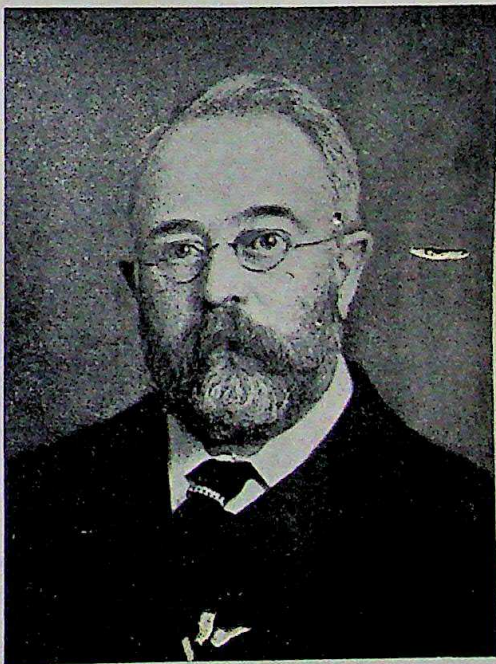
APRIL 1907

THE fusion of the medical societies of London into one strong body that should be able, like the French Académie de Médecine, to speak with authority in the name of the profession on scientific questions, has often been advocated by *The Practitioner*. The Editor, therefore, hails with satisfaction 'the amalgamation, partial as it is, that has been effected. It is not indeed the organization of which we have dreamed, but it may perhaps be looked upon as an intermediate stage in its development. . . . While rejoicing that the first step to a union of our scientific forces has been taken, we cannot help regretting that it has been decided to call the new body the Royal Society of Medicine. It is almost a colourable imitation of the title of the greatest and most ancient of our scientific associations, and it is to be feared that it will lend itself to misapprehension and even misuse. The public cannot be expected to discriminate very exactly between one Royal Society and another, and unfortunately it is not altogether inconceivable that some members might not take the trouble to dispel the confusion'.

'Philosophers have had much difficulty in providing a satisfactory definition of man [according to "Notes by the Way"]. Plato's "biped without feathers" failed to stand a practical test. . . . There is room, therefore, for a new definition of man, and we venture to propose "an animal deluded by advertisement" as meeting the requirements of the case. Man changes in everything else; he has rid himself of many superstitions, but he is still as much the prey of the advertiser as he was when he allowed himself to be gulled by the records of cures inscribed on the walls of the temples of Asklepios in ancient Greece. Many of these are exactly in the style of the infallible nostrums which are pillars of support for our free and independent press of the present day. And wherever we strike the trail of the advertiser through the ages, it is always the same kind of thing'.

The first of the 'Original Communications' entitled 'The Treatment of Post-Partum Haemorrhage' introduces a note of novelty, for its author, G. E. Herman, F.R.C.P., F.R.C.S., Consulting Obstetric Physician to the London

Hospital, had been asked by the Editor 'to criticise three articles on the subject, which appeared in the issues of August and November 1906, and February 1907'. George Ernest Herman was appointed Obstetric Physician to 'The London' in 1883. He was a brilliant operator and a fine clinical teacher. Entertained to dinner by his former Residents in July 1903 upon being elected consulting obstetric physician, he



George Ernest Herman, F.R.C.P., F.R.C.S.
(1849-1914)

began his speech: 'As has been well said, there is more joy over one senior that resigneth, than over ninety and nine just appointed persons'.

John Cowan, M.D., Physician to the Royal Infirmary, Glasgow, discusses 'The Myogenic Theory' of the cardiac action; Frederick Langmead, M.D., M.R.C.P., Physician to Out-patients, Paddington Green Children's Hospital, takes as his subject 'The Relationship between Simple Posterior Basic Meningitis and

Cerebro-spinal Fever'; and A. F. Hertz, M.B., M.R.C.P., Demonstrator of Physiology and Pharmacology at Guy's Hospital Medical School, presents 'Notes from Germany on the Value of Röntgen Rays in Medical Diagnosis'.

'Carlyle somewhere says that, by careful search, it might be possible to discover the greatest fool extant at any given time. It might be difficult to say who was the greatest quack that ever lived, but if matchless impudence were to be accepted as the test, a well-founded claim might be made on behalf of James Graham, the high priest of the Temple of Health of which the Goddess was Lady Hamilton. . . . Thither at one time flocked the fashionable society of London, to listen to what many of them must have known to be quackery of the vilest kind, and to be treated by methods openly intended for the stimulation of lust rather than for the healing of disease'.

A number of popular books are reviewed this month. Walter E. Dixon's 'A Manual of Pharmacology' is highly commended 'to all practitioners of medicine, who take an interest in the action of drugs'. Of 'Recent Advances in Physiology and Bio-Chemistry', edited by Leonard Hill, the reviewer writes: 'This excellent work, which is admirably produced, may be recommended to all medical men, who desire to acquaint themselves with the latest views upon the subjects'. 'A Treatise on Surgery' by

George Ryerson Fowler 'seems to us somewhat unequal, and we may perhaps be allowed to enter a protest against its excessive weight, which is, we believe, due to the free use of bismuth in the preparation of the paper'.

'Practical Notes' quote from an article on 'Nocturnal Enuresis' in *Gazette Médicale de Paris*:—'The most frequent causes of this bad habit are hyperacidity of the urine and abnormally deep sleep. When the former is proved to be present, it is usually enough to give alkaline remedies in order to obtain a cure. When the wetting occurs as a consequence of too deep a sleep, the best measure to adopt is systematic awakening of the child. In order to carry out this method thoroughly in the case of inveteracy, and to force the child to accustom to waking up at the critical moment, the following procedure has been tried with success: The child lies upon a mattress composed of two layers of metallic tissue separated by a dry cloth. . . . Each of these layers is connected by a wire to the working part of a loud electric bell placed above the bed. As soon as the first drop of urine has damped the cloth, and so made contact, the bell rings furiously, and wakens the sleeper. By reflex inhibition, the action of the bladder is stayed. From two to five repetitions of this experience are said to be sufficient for a radical cure'.

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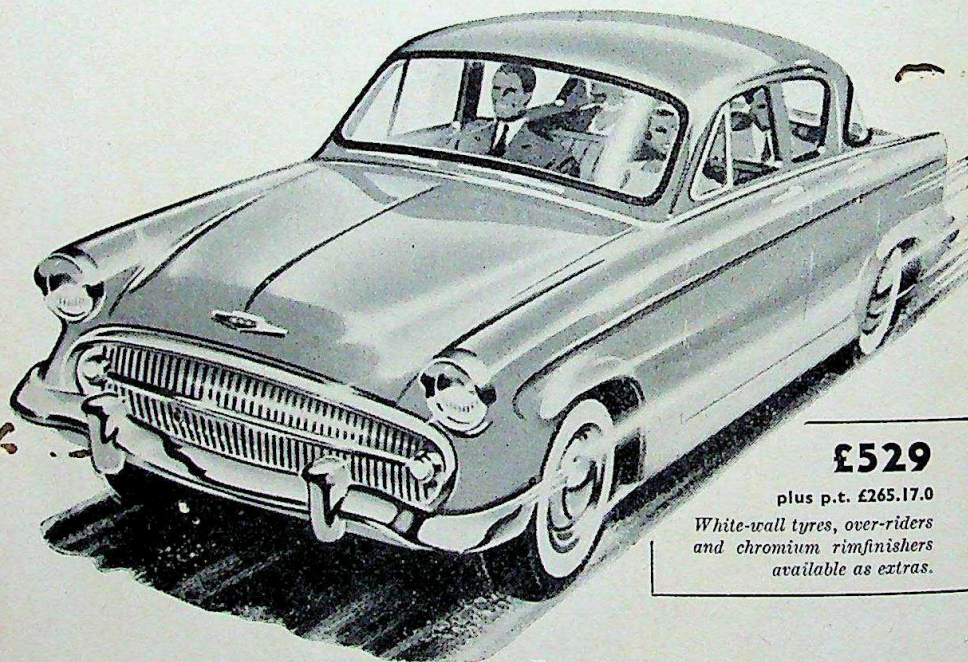
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MOTERING NOTES

Selecting a New Car

By ROBERT NEIL

THE recent announcement of the new Vauxhall Victor has given fresh impetus to the inevitable discussions about the ideal car for a practitioner. An increasing number of doctors throughout the country must be finding that the ever-rising overhead costs in their practices indicate that it would be wise to run a smaller and more economical car than has been the general rule. Because of the well-deserved reputation for economy enjoyed by all Vauxhall models the new Victor has been hailed as the solution to many motorists' problems. The makers of this new car will, I hope, forgive me if I point out to readers that when buying such an important and expensive item of equipment as a motor car it is better not to be egged on by a sudden burst of enthusiasm, but to study the pros and cons with extreme *sang froid*.

THE CAR FOR THE JOB

What I think many motorists forget, and perhaps practitioners more than others, is the particular purposes for which their car is most important. Few would sympathize with a commercial traveller who used his firm's money to buy a car which was perfect for the occasional week-end trip, but was quite unsuitable for the business for which it was intended. It is fatally easy for the driver to be so impressed by the performance, or the handiness of the controls, to forget such points as visibility from the rear seats—even though his child might suffer from car sickness—or the dimensions of the luggage boot. It is essential to go through any prospective new car's specification with a most analytical and suspicious mind. I feel that many doctors who use their cars day after day will agree with me that one of the greatest irritations is having to put their car off the road every now and then to have essential greasing and servicing carried out. It is therefore necessary before deciding on an individual car to check by means of the instruction book how many, and at what intervals, points require attention with the grease gun. When such cars as Bentley, Rolls-Royce and Rover are run this is no problem, as the use of centralized chassis lubrication systems or the use of rubber bearings and sealed oil-packed bearings, increases considerably the intervals between servicing.

One point which some motorists seem to forget when choosing a new car is the number of doors which will best suit their purpose. If the rear seat is only occupied occasionally it is worth while considering the purchase of a

two-door saloon, which has the other advantages that the driver's door will be wider than normal, making entry or exit easier, whilst a motorist with very young children is spared the worry of a rear door opening unexpectedly. The four-door saloon however, is probably better if the rear seat is used much, as the disadvantage of the two-door body lies in the necessity for either the driver or the front passenger to get out to free the way for a passenger from the rear compartment. I agree that this may seem a very simple point when one reads it, but there must be many motorists who would agree that they have often forgotten it—to their sorrow.

On more technical points there is probably even more confused thinking. Merely because a friend, of whose driving style and habits they know nothing, has had excellent service from a particular car, many motorists follow his example blindly only to find disillusionment. The friend might easily be a driver who enjoys driving and gear changing, and had selected a high-gear car with a four-speed gearbox. This would be unsuitable for our hypothetical purchaser, whose real wants would best be filled by a smooth effortless car with a three-speed gearbox, which would give him labour-free driving.

THE VAUXHALL VICTOR

Bearing these thoughts in mind it is of special interest to study the specification of the new Vauxhall Victor (fig. 1, 2). As this car is obviously intended for very large-scale production, which means that it must please a wide section of the motoring public, it is perforce a compromise, but a remarkably successful one. For many years now all Vauxhall models have had a justified reputation for economy, to such an extent that there is no car of equivalent performance, size and price which can equal their fuel consumption figures, and there is every reason to believe that this new model will surpass its bigger sister cars. At the moment of writing I have not had the opportunity of carrying out a test, but it can be accepted that the fuel consumption obtained by owners will vary between 28 and 35 m.p.g.

One of the conveniences of the modern car which many motorists have come to regard as an essential is the heating and demisting system. It is of interest that the type fitted to the Vauxhall is most efficient, and if the trouble is taken by the owner to blank off the radiator appropriately during the winter months—so that working temperature will be quickly

THE PRACTITIONER

reached—this is, in itself, a great boon to practitioners, who might be called out in the middle of the night.

As a large proportion of the Vauxhall Victor's power is produced at relatively low engine speeds the gears do not require to be used so often as on many other cars; this undoubtedly reduces the effort of driving. Bottom gear need only be used for getting away from rest, whilst second gear can be used down to any speed other than a full stop. This new car is the first car built in Europe to use a panoramic windscreen, and the forward vision is remarkably good, providing a wide angle without the interference of windscreen pillars. This benefit carries with it a slight disadvantage. As it is a relatively small car the bringing back of the windscreen sides causes a reduction in the effective door space; about a quarter of the front

formance with economical running, it is likely to become a very popular car on British roads, as well as elsewhere.

PARKING PROBLEMS

Readers who live or work in London will be well aware of the parking problem, which faces both the Government and the everyday motorist. It is unfortunate that the schemes of the Minister of Transport seem to be based entirely upon restriction and obstruction, rather than on a single common-sense approach to the problem. Too many motorists, in my opinion, in their estimable attempts to be good citizens, sit down under the most inept and shortsighted of policies. It is entirely the responsibility of the Minister of Transport to provide the means for the motor vehicle to continue to contribute to the business and

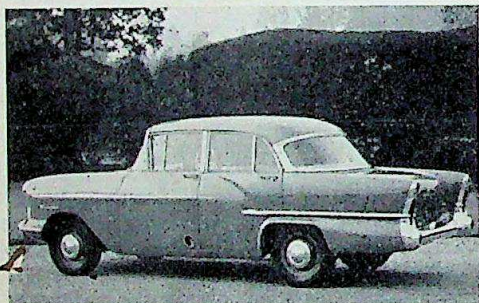


FIG. 1.—The new Vauxhall Victor.

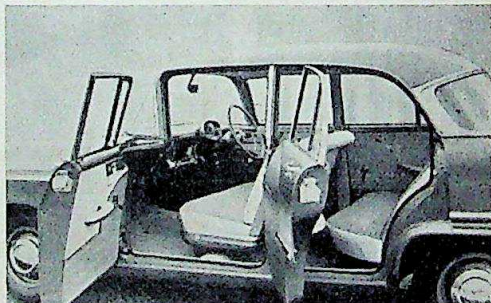


FIG. 2.—Interior of the new Vauxhall Victor.

door width is made ineffective by the intrusion of the windscreen (fig. 2). This, however, is a point which will probably be forgotten after one has driven the car for a few days.

TOO MUCH CHROMIUM

The point on which the Victor can be justifiably criticized is in the lavish use of chromium as mere ornamentation. The constant worry of keeping the plating in a presentable condition is one that the average busy motorist would be happier without. The rectangular lines of the rear wings and the luggage boot give two benefits. The horizontal top line of the rear wings allows them to be seen easily by the driver, with the result that reversing can be a very accurate manoeuvre, whilst the box-like angularity makes the luggage boot remarkably roomy. For styling reasons the bumpers on the new Vauxhall are not separate from the bodywork (fig. 1) and, although this improves the appearance, it may have the disadvantage that minor bumps—as are likely to be received in a car park—could be transmitted to the bodywork itself.

As the Vauxhall Victor is being offered at a low price, and combines a 75 m.p.h. per-

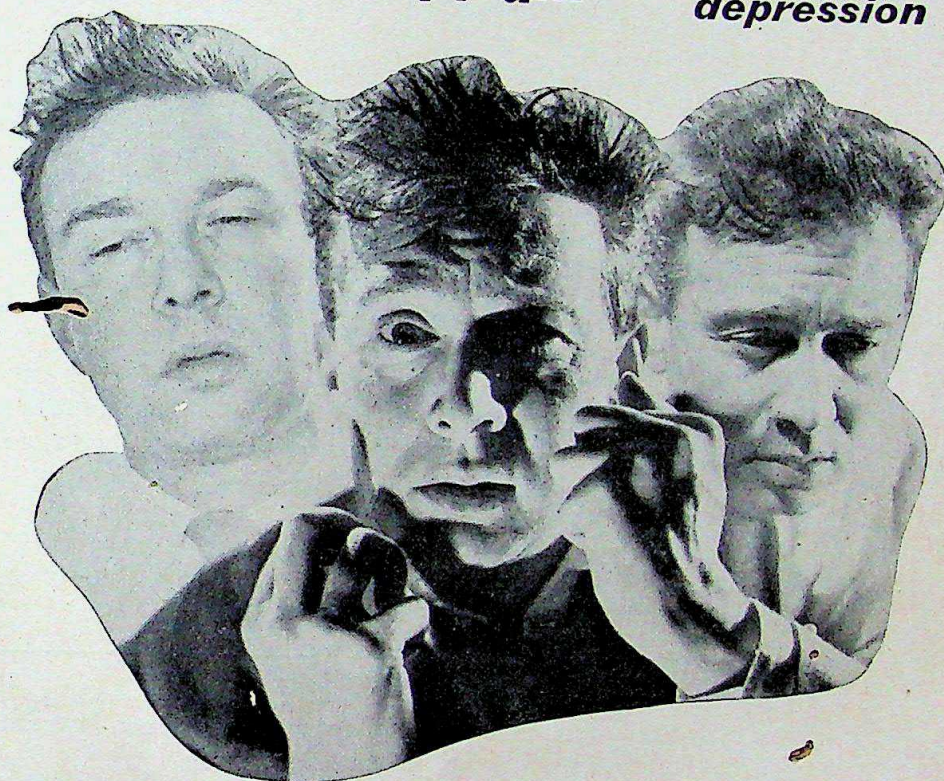
professional life of the country, and merely to say that motor cars will not be allowed in London is a childish evasion of the problem. The Committee on Parking in the Inner Area of London has suggested that in the future only 50 per cent. of the cars entering London in normal times should be allowed. Many readers will recall the conditions which ruled during the railway strike of 1955. The sudden increase of motor cars entering London caused complete confusion for a few days, but realistic action by the police produced a flow of traffic considerably better than existed with less cars before the strike. This was entirely due to the fact that it was realized that an emergency existed, and the police urged the traffic in to moving as fast as is common in Paris.

The lack of forethought demonstrated by the Government's predecessors is no excuse for following their example. The Minister of Transport should institute at once a vigorous policy for speeding up traffic as such, and to provide vast extra parking spaces around the perimeter of Inner London—not, as has been suggested, at Underground Stations about 10 to 15 miles from London.

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TRAVEL NOTES

Taking the Family Abroad

By PENELOPE TURING

JUDGING by the letters which I have received, a large number of readers are considering the question of a family holiday on the Continent and would like details on the pros and cons of different countries and districts. Here therefore are a few facts and suggestions which I hope may be of some use.

In general the basic principles seem to me to be these: for children up to the age of, let us say, 14, sea and a good bathing beach are almost essential; for parents reasonably comfortable accommodation, good food and a place where the children are welcome are vital to the success of any holiday; and finally the shorter the journey the better, both from the financial angle and for the sake of the family's nerves.

THE BRITTANY COAST

Nearly all these qualifications can be found on the coasts of Brittany. Here there are wonderful beaches with wide, flat sands and some of the safest bathing to be found anywhere. I was talking about this to a man who knows France better than many of its natives, and speaking from experience with his own child he put Brittany before anywhere else. The fishing villages (fig. 1) and small seaside resorts west of St. Malo are ideal for a young family, and the average one-star hotels can be relied on for cleanliness and excellent cooking. They are bare, of course, often simple in the extreme, but children are always welcomed and often can do no wrong in the eyes of the proprietors, which certainly helps the holiday atmosphere. St. Briac, just west of St. Malo and Dinard, is a charming example of

it is straightforward. You take the night boat from Southampton to St. Malo (about 10 hours) and from there a special coach service runs to

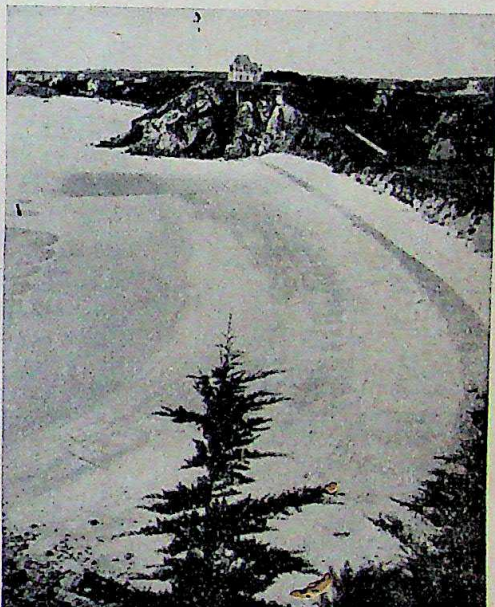


FIG. 2.—Morgat on the coast of Brittany.

the more important centres along the north coast: St. Cast, Erquy, Le Val André, St. Brieuc, Trébeurden, Trégastel and Perros-Guirec. Alternatively you can fly to Dinard.

On the west coast there are more attractive places: Morgat (fig. 2), for example, and Bénodet where the Hotel à l'Ancre de Marine offers really first-class cooking.

My own first trip abroad at the age of four was to another and far more sophisticated French resort, Le Touquet. The bathing was not, I think, very safe, for coastguardmen were on duty to rescue over-adventurous swimmers. I have not been there since, but a friend tells me that it is now much more of a family centre with special games and P.T. organized for children on parts of the beach.

THE BELGIAN COASTAL TOWNS

The Belgian coastal towns are another happy hunting ground for children, and the journey is shorter than that to Brittany. The day crossing from Dover takes 3½ hours to Ostend, from which an electric tram service runs all along the



FIG. 1.—The fishing fleet at Concarneau, Brittany.

these little towns with lovely sands and a succession of fascinating bays, each with its rock pools. The journey is not, perhaps, very short, but

THE PRACTITIONER

coast. There are 40 miles of unbroken sands, and the seaside towns vary to suit most tastes. Personally I would prefer to get away from the bustle and day trippers of Ostend to, perhaps, Knocke with its Siamese twin, Le Zoute. These are the easternmost resorts close to the Dutch border, and one can easily make a day trip across to Flushing and on to Middelburg. Knocke has attractions for all ages: a casino which is the social centre, several golf courses, numberless tennis courts, and so on.

As a contrast one of the quietest places along this coast is Brédene, only ten minutes by tram from Ostend quay. Here there is a good sand beach backed by dunes, a few hotels and pensions and a golf course not far away; a typical small family resort. Just a little farther east of this is another small place, Le Coq-sur-Mer. This is a cheerful little open-air village where there is only a short promenade and every villa has its garden, for Le Coq considers flowers its hallmark. West of Ostend, Middelkerke is a good place for children, with a 6-mile promenade and fine sands.

Another advantage of this stretch of coast is that several of the most beautiful and interesting cities of Belgium are within easy reach by day trip. Bruges which somehow never loses its fascination however many trippers crowd its streets or walk through the timeless peace of the Béguinage, Ghent, and even Brussels. From Knocke Brussels is only one-and-a-half hours by train, and a day there makes an ideal contrast to the seaside, including perhaps a superb and expensive lunch at one of the first-class restaurants among the old guild houses of the Grand' Place.

ITALIAN SUNSHINE

By this time someone has probably remarked that sunshine is almost as important as sea, and Belgium and Brittany are too far north to guarantee it. For warmth and sunshine Italy is of course one of the best choices, and with young children I would advise flying out. The boat and train journeys take 27 hours or more, which is a long trip even for an adult, whereas by air the time is reduced to 3 or 4 hours, plus of course journeys to and from the airport.

At the western end of the Italian Riviera are San Remo (fig. 3) and Alassio; farther south and just north of Pisa is Viareggio, and on the Adriatic coast a whole string of places south of Venice: Rimini, Riccione, Cattolica and others. All these have wonderful beaches which are packed with people at the height of the season, a good range of accommodation and as much colour and warmth as anyone could wish; in July and August the average 24-hour temperature is seldom below 70°F.

HOLIDAY CAMPS

Where economy is a vital factor and sea and sunshine outweigh the charms of luxury, a holiday camp is worth consideration. Cooks have their St. Aygulf Holiday Village on the French Riviera between St. Raphael and St. Tropez where you can stay in individual chalets (with cold running water), and cafeteria meals are provided in a central clubhouse. Many people find this solves the problem of an inexpensive family holiday, for the charges are very modest.



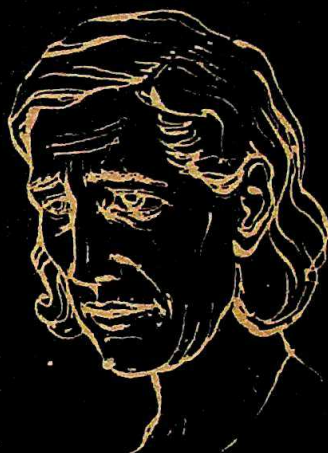
FIG. 3.—The Beach at San Remo.

There are, of course, literally thousands of other places on the Mediterranean shores and elsewhere which are ideal for children and grown-ups alike: the Spanish Costa Brava and Costa del Sol, the coast of Portugal, and so on. I myself would not recommend taking very small children, certainly not those under five years old, to the out-of-the-way places because of local difficulties such as shortage of fresh milk, or drinking water problems, which may crop up. But for older ones with a taste for adventure there is really no limit to the range of possible holidays.

One thing, however, has to be borne in mind: school holiday times are much the same all over Europe and they coincide with the peak period for adult tourists also. This means that bookings are heaviest and prices highest at that time of year, so that it is important to make reservations at hotels, on planes and for ships' berths as early as possible.

From April 1 to October 31 there are daily flights to Dinard (1 hour, 55 minutes) for a return fare of £15 3s.; from the beginning of June to mid-September mid-week 15-day excursion returns cost £12 10s. By boat the return fares Southampton-St. Malo are £10 11s. 3d. 1st class, £7 13s. 9d. 2nd class. For Belgium the boat crossing Dover-Ostend is £5 2s. return 1st class; £3 18s. 2nd class. From May till September there are direct flights to Venice on Thursdays and Saturdays (2 hours, 55 minutes) for £41 5s. return; £33 by night flight. To Nice (for San Remo) the flight takes 4 hours, 25 minutes, return fare £37 15s. A ten days' inclusive holiday at Cook's Holiday Village costs £24 15s.; children of 10-15 and 4-10 years £22 15s. and £19 15s., respectively.

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101, GREAT RUSSELL STREET, LONDON, W.C.1

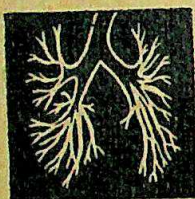
Telephone : MUSum 2042-3-0626.

Telegrams : Taxolabs, Phone, London



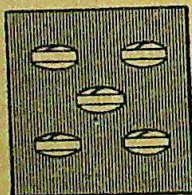
Piriton

the safe, low dosage antihistamine



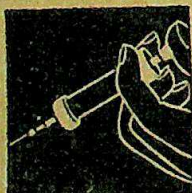
FOR EXPECTORANT COUGH THERAPY

PIRIEX, a combination of an antihistamine of low toxicity with accepted expectorant drugs, effectively liquefies tenacious sputum and aids its prompt removal. Piriex is suitable for administration to children and adults.



FOR ROUTINE ANTIHISTAMINIC THERAPY

PIRITON TABLETS containing 4 mg. of Piriton maleate, an improved antihistamine, provide distinct symptomatic relief of allergic symptoms in hay fever, vasomotor rhinitis, urticaria, angio-neurotic oedema, insect bites, etc.



FOR PARENTERAL ANTIHISTAMINIC THERAPY

PIRITON INJECTION, containing 10 mg. Piriton maleate per. c.c is indicated for the prevention and treatment of reactions due to penicillin, other parenteral medications and blood transfusions.



FOR PÆDIATRIC ANTIHISTAMINIC THERAPY

PIRITON SYRUP is the ideal form of administration for antihistaminic therapy to children of all ages. It is compatible with many drugs and its use as a base is often advisable when it is desired to administer medications to which the patient is known to be allergic.

CS6/627/630

ALLEN & HANBURY'S LTD. LONDON E 2

TELEPHONE: BISHOPSGATE, 3201 (20 LINES); TELEGRAMS: "GREENBURYS, BETH, LONDON"

Completed
1999-2000

